UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

June 25, 2001

SUBJECT: **Thiophanate-Methyl:** HED Revised Preliminary Risk Assessment for the Reregistration Eligibility Decision (RED) Document. Chemical No.102001. Barcode: D275774

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Attached is HED's revised preliminary risk assessment of the fungicide, thiophanate-methyl, for purposes of issuing a Reregistration Eligibility Decision (RED) Document for this active ingredient. This assessment aggregates the risk estimates for carbendazim or methyl-2-benzimidazole carbamate (MBC), which is a metabolite of thiophanate-methyl, and is also registered for use in residential settings as a paint additive and for tree injection. Although MBC is also an environmental metabolite of benomyl, in April 2001, the benomyl registrant requested voluntary cancellation of all benomyl-containing products, with sales and distribution proposed to cease by December 31, 2001 (http://www.dupont.com, April 19, 2001). Therefore, potential exposures to MBC from benomyl use were not evaluated in this assessment. Cumulative risk assessment considering risks from other pesticides or chemical compounds having a common mechanism of toxicity is not addressed in this document. This assessment incorporates the "error-only" comments received from the registrant during Phase I of the Tolerance Reassessment Advisory Committee (TRAC) process. The disciplinary science chapters and other supporting documents for the thiophanate-methyl RED are also included as attachments as follows:

Report of the Hazard Identification Assessment Review Committee. J. Doherty (11/6/200; HED Doc No. 014370 for thiophanate-methyl) and D. Smegal (8/2/99, HED Doc No. 013602 for MBC)
Report of the FQPA Safety Factor Committee. Brenda Tarplee (For thiophanate-methyl: October 25, 2000; HED Doc No. 014363 and for MBC: July 1, 1999; HED Doc No. 013544 for MBC)
Revised Toxicology Chapter for Thiophanate-methyl. Deborah Smegal and Linnea Hansen, March 15, 2001. D272850.
Toxicology Chapter for Benomyl and Carbendazim. D. Smegal. January 31, 2001. D272363.
Occupational and Residential Exposure Assessment for Thiophanate-methyl. Gary Bangs (March 15, 2001, D271922)
Occupational and Residential Exposure Assessment and Recommendations for the Risk Assessment Document for MBC. G. Bangs, March 2001, D273465.
Anticipated Residues, Acute and Chronic Dietary Risk Assessments for Thiophanate-methyl (TM) and its Metabolites Methyl 2-benzimidazolyl carbamate (MBC) and 2-Aminobenzamidazole (2-AB). S. Piper, March 2001. D272944.
Revised Product and Residue Chemistry Chapter. Jose Morales (March 15, 2001; D272013)
Tier 1 Estimated Environmental Concentrations for Thiophanate-methyl and its major degradate, MBC. R. Pisigan/I. Abdel-Saheb, 1/19/2001.
Additional Estimated Environmental Concentrations for Thiophanate-methyl and its major degradate, MBC for application on Turf and Onions. R. Pisigan/I. Abdel-Saheb, 4/11/2001.
Review of Thiophanate-Methyl Incident Reports. J. Blondell and M. Spann. August 15, 1997. D230959.

HED's Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicological database for thiophanate-methyl on September 26, 2000 (memorandum dated November 6, 2000) and its primary metabolite, carbendazim or MBC on June 1, 1999 and February 20, 2001 (memorandum dated March 2001) and selected toxicological endpoints for acute oral, chronic oral and for short-, intermediate and long-term dermal and inhalation exposure risk assessment. HED's FQPA Safety Factor Committee reviewed the hazard and exposure data for thiophanate-methyl on October 16, 2000 and recommended that the FQPA Safety Factor (as required by Food Quality Act of August 3, 1996) be reduced to 3X in assessing the risk posed by thiophanate-methyl (memorandum dated October 25, 2000), and retained at 10X in assessing the risk posed by MBC (memorandum dated July 1, 1999).

REVISED PRELIMINARY HUMAN HEALTH RISK ASSESSMENT:

THIOPHANATE-METHYL

June 25, 2001

Health Effects Division

Office of Pesticide Programs

U.S. Environmental Protection Agency

1.0 EXECUTIVE SUMMARY

The Health Effects Division (HED) has conducted a Preliminary Human Health Risk Assessment for the active ingredient thiophanate-methyl for the purposes of making a reregistration eligibility decision (RED). The toxicological database is not complete, and several studies have been requested. Residue chemistry requirements are outstanding, including storage stability data to support the residue data for plant and animal commodities. The Agency has insufficient data to assess handler or post-application exposure during mixing, loading, or applying pesticides for seedling or bulb dip treatment, and additional data are requested to support these uses.

Thiophanate-methyl [dimethyl [(1,2-phenylene)bis(iminocarbonothioyl)] bis(carbamate)] is a systemic fungicide registered for use in a wide variety of agricultural, ornamental, and residential settings. Thiophanate-methyl is manufactured by Nippon Soda Company Ltd. of Japan, under the trade name Topsin M®. The registrants are Elf-Atochem North America Agrichemicals, NISSO TM LLC and Gowan Pacific LLC. There are 36 active registrations and 22 special local need registrations. There are approximately 54 tolerances. Major food/feed crops include: almonds, apples, dry beans, green beans, peaches, potatoes (seed pieces), soybeans, sugar beets, and wheat. Non-agricultural uses include ornamentals, turf (sod farms, residential and recreational lawns), greenhouses, interior scapes, landscaping, and nursery use. There is a potential for exposure from agricultural, commercial operator, and residential uses. The estimated annual usage is 454,000 lbs ai/year (weighted average) to 769,000 lbs ai/year (estimated maximum) for agricultural uses of thiophanate-methyl. Non-agricultural use estimates (i.e., residential and golf course use) are not available. Agricultural usage has increased nearly 150% in recent years.

Thiophanate-methyl formulations registered for use include dust (D), granular (G), wettable powder (WP), water-disperable granular (WDG), and flowable concentrate (FlC) and emulsifiable concentrate (EC) formulations, and ready-to-use liquid ranging from 1.65% to 90% active ingredient (a.i). The dust formulation may be applied to potato seed-pieces at planting and the granular formulation may be applied as an in-furrow application to beans at planting. The remaining products may be applied as an in-furrow application at planting to onions (WP and WDG) or as postemergence broadcast applications to all other labeled crops using ground or aerial equipment.

Tolerances for residues of thiophanate-methyl in/on plant and livestock raw agricultural commodities (RACs) are <u>currently</u> expressed in terms of thiophanate-methyl, its oxygen analogue [dimethyl-4,4'-o-phenylene bis(allophanate)], and its benzimidazole-containing metabolites (calculated as thiophanate-methyl). However, thiophanate-methyl is metabolized or hydrolyzed under aqueous conditions to its major metabolite carbendazim or MBC (methyl 2-benzimidazole carbamate), which is also a systemic fungicide. Hence, some environmental residues in food are present as MBC. Consequently, the HED Metabolism Committee recently recommended that the tolerance expression in 40 CFR §180.371 be modified to include residues of thiophanate-methyl, and carbendazim or MBC (methyl 2-benzimidazole carbamate) in plant and animal commodities. Based on the Metabolism Committee recommendation, the residues of concern evaluated in the dietary risk assessment are thiophanate-methyl, MBC and 2-AB (2-amine-1-H-benzimidazole) in plant commodities, and thiophanate-methyl, MBC, and the hydroxylated metabolites of MBC (4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S) in animal commodities. There are two separate analytical methods that quantify the residues of concern, one method for plant commodities and one method for animal commodities (i.e., thiophanate-methyl, MBC and 2-AB in plants and thiophanate-methyl, MBC, 5–OH-MBC and 4-OH-MBC and 5-OH-

MBC-S in animals). Based on the revised tolerance expression, the current data collection methods are acceptable for all residues of concern in plant and animal commodities. However, the current enforcement method requires radio-validation, EPA method validation, and an independent laboratory validation of the method. Independent laboratory method validation was completed and has been recently submitted to HED. All residues of concern are evaluated in this risk assessment.

Thiophanate-methyl is rapidly degraded to MBC under environmental conditions. Therefore, MBC residues are present in food, drinking water and on lawns and home-grown fruit following thiophanate-methyl use. Other metabolites of concern in food commodities are 2-AB, and hydroxylated metabolites of MBC. This report estimates the exposures and risks associated with both thiophanate-methyl and its major metabolites: MBC and 2-AB in plant commodities; and MBC, 4-OH-MBC, 5-OH-MBC and 5-OH-MBC-2 in animal commodities. Exposures to both thiophanate-methyl and MBC are evaluated for residential uses of thiophanate-methyl (i.e., lawn use, and harvesting treated fruit). In addition, MBC is registered for tree injection and as a fungicide/preservative in paints, coatings, plaster and adhesives in residential settings. Therefore, residents could be exposed to MBC via dermal and inhalation exposure during painting activities, and via inhalation to vapors in painted rooms. Residential exposures resulting from tree injection uses are considered to be negligible. Aggregate exposures to MBC (and metabolites of concern) resulting from thiophanate-methyl, and MBC use have been estimated and evaluated in this report.

Hazard: Both thiophanate-methyl and MBC are of low toxicity following acute oral, dermal and inhalation exposures (toxicity categories III/IV). Thiophanate-methyl is classified as a skin sensitizer, while MBC is not a skin sensitizer. Thiophanate-methyl and MBC share some common toxicological effects, including developmental and liver effects. In all animal species tested, the most sensitive toxicological effect is liver toxicity following subchronic and chronic oral exposure to both thiophanate-methyl and MBC. The thyroid gland is also one of the most sensitive target organs for thiophanate-methyl following oral exposures. Thiophanate-methyl is generally less toxic than MBC for adverse developmental effects, and adverse liver effects following chronic exposure. Dogs appear to be the most sensitive species to subchronic and chronic oral exposure. Both thiophanate-methyl and MBC have been associated with an increased incidence of mouse liver tumors following chronic oral exposure. MBC has weak mutagenic activity that is primarily attributed to adverse effects on cellular spindle apparatus. In addition, both thiophanate-methyl and MBC cause aneuploidy (i.e., abnormal number of chromosomes).

Both thiophanate-methyl and MBC induce developmental toxicity. The developmental effects of MBC occurred in the absence of maternal toxicity, indicating increased fetal susceptibility. Fetal effects from thiophanate-methyl exposure include an increase in supernumerary ribs, and reduced fetal weight. In rats, adverse fetal effects attributed to maternal MBC exposure include decreased body weight, increases in skeletal variations and malformations, and ocular and brain malformations. MBC is associated with adverse reproductive effects, including adverse testicular effects such as reduced sperm counts, reduced testes size, and testicular pathology (i.e., atrophy and degeneration of the seminiferous tubules). Other reproductive effects observed only in the presence of parental toxicity include reduced pup weights.

Toxicity Endpoints. The toxicity endpoints used in this document to assess hazards include acute dietary and chronic dietary reference doses (RfDs), and short-, intermediate- and/or long-term incidental oral, dermal and inhalation doses. HED's Hazard Identification Assessment Review Committee (HIARC) developed toxicity endpoints for both thiophanate-methyl and its primary metabolite MBC based on exposure concerns. Because thiophanate-methyl and MBC cause adverse developmental effects, HIARC identified two acute dietary reference doses (aRfDs) for each compound, one for females of child bearing age (13-50 years) and one for the general population, including infants and children.

Acute and Chronic RfDs. For thiophanate-methyl, HIARC identified aRfDs of 0.2 mg/kg/day and 0.4 mg/kg/day for females 13-50 yrs and the general population, respectively. The female 13-50 year acute RfD is based on a no-observed-adverse effect level (NOAEL) of 20 mg/kg/day for an increased incidence of supernumerary ribs in fetuses at a lowest-observed-adverse effect level (LOAEL) of 40 mg/kg/day in a rabbit developmental study. The thiophanate-methyl aRfD for the general population is based on a NOAEL of 40 mg/kg/day for tremors observed 2-4 hours following a single 200 mg/kg/day dose exposure in dogs. The thiophanate-methyl chronic RfD (cRfD) is 0.08 mg/kg/day based on a NOAEL of 8 mg/kg/day for adverse thyroid effects and decreased body weight observed at 40 mg/kg/day in a 1-year dog study. The acute dietary RfDs for MBC are 0.1 mg/kg/day and 0.17 mg/kg/day for females 13-50 yrs and the general population, respectively, based on adverse fetal effects, and testicular effects, respectively. The chronic RfD of 0.025 mg/kg/day for MBC is based on a NOAEL of 2.5 mg/kg/day for adverse liver effects from a 2-year dog study (LOAEL is 12.5 mg/kg/day. An uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variability) was applied to the NOAELs to obtain all acute and chronic RfDs, except for the general population acute RfD for MBC, which has a total uncertainty factor of 300 (extra factor of 3) to account for the absence of a NOAEL.

Short and intermediate-term incidental oral endpoints: For thiophanate-methyl and MBC, HIARC identified a short-term oral NOAEL of 10 mg/kg/day based on decreased body weight and food consumption following thiophanate-methyl exposure of 20 mg/kg/day. This endpoint is also applicable to intermediate-term thiophanate-methyl exposures. For intermediate-term MBC exposures, HIARC identified an oral NOAEL of 11 mg/kg/day (rounded to 10 mg/kg/day) based on adverse liver effects in a subchronic dog study with MBC at 35 mg/kg/day.

Dermal Endpoints. For thiophanate-methyl, the short- and intermediate-term dermal endpoint is based on a NOAEL of 100 mg/kg/day based on decreased body weight and food consumption seen at 300 mg/kg/day in a 21-day dermal rabbit study. The long-term dermal endpoint is based on an oral NOAEL of 8 mg/kg/day from the chronic dog study that observed adverse thyroid effects and decreased body weight at 40 mg/kg/day. Because an oral NOAEL was selected, a 7 percent dermal absorption factor was used, based on a comparison of the oral developmental toxicity study and a 21-day dermal toxicity study in the same species (rabbit) with similar endpoints (decreased food consumption). For MBC, HIARC identified short- and intermediate term NOAELs of 10 mg/kg/day based on adverse fetal effects noted in a rat developmental study at 20 mg/kg/day. The long-term NOAEL is 2.5 mg/kg/day based on liver toxicity noted in a 2-year dog study at 12.5 mg/kg/day. Because oral NOAELs were selected, a 3.5 percent dermal absorption factor was used for MBC, based on a rat dermal absorption study with benomyl.

Inhalation Endpoints. For thiophanate-methyl, the short- and intermediate-term inhalation endpoints are based on an oral NOAEL of 10 mg/kg/day based on decreased maternal body weight and food consumption in the rabbit developmental study at 20 mg/kg/day. The long-term inhalation endpoint is based on an oral NOAEL of 8 mg/kg/day from the chronic dog study that observed adverse thyroid effects and decreased body weight at 40 mg/kg/day. Because an oral NOAEL was selected a 100% inhalation absorption factor (relative to oral absorption) was used in route-to-route extrapolation. For MBC, the short-, and intermediate- term inhalation NOAEL is 0.96 mg/kg/day from a 90-day rat inhalation study with benomyl that observed adverse respiratory effects at 4.8 mg/kg/day. This study was selected to assess MBC in the absence of inhalation data for MBC.

Cancer. Thiophanate-methyl is classified as "likely to be carcinogenic to humans", while MBC is classified as a possible human carcinogen (group C). Both chemicals and are associated with hepatocellular tumors in certain strains of mice. HED estimated a unit risk Q_1^* of 1.38×10^{-2} $(mg/kg/day)^{-1}$ for thiophanate-methyl based on a dose-dependent increase in liver tumors in male CD-1 mice. HED estimated a unit risk Q_1^* of 2.39×10^{-3} $(mg/kg/day)^{-1}$ for MBC based on hepatocellular (adenoma and/or carcinoma) tumors in female CD-1 mice exposed to MBC.

FQPA Safety Factor: The Food Quality Protection Act (FQPA) Safety Factor Committee determined that the FQPA 10X safety factor should be reduced to 3X for thiophanate-methyl and retained at 10X for MBC. The factor is to be applied to acute and chronic dietary exposures. In accordance with HED policy, a RfD modified by a FQPA safety factor is a population adjusted dose (PAD)[1] .

The **FQPA factor is necessary, but reduced to 3X for thiophanate-methyl** due to an incomplete toxicity database (acute and subchronic neurotoxicity studies are required due to evidence of neurotoxicity) and the requirement for a developmental neurotoxicity study has been ‘reserved’. However, the available data provided no indication of increased susceptibility *in utero* exposure in the developmental studies in rats and rabbits or following pre-/postnatal exposure in the multi-generation reproduction studies in rats; and the dietary (food and drinking water) and non-dietary exposure assessments will not underestimate the potential exposures for infants and children from the use of thiophanate-methyl. The 3X FQPA safety factor is applicable for all **risk assessments for all population subgroups**.

The **10X factor was retained for MBC** due evidence of increased susceptibility following *in utero* exposure of MBC in the prenatal developmental toxicity study in rats and rabbits; and the need for developmental neurotoxicity studies in rats for MBC. The 10x FQPA safety factor is applicable for all **risk assessments for females 13-50 years, Infants, and Children** (1 - 6 years and 7-12 years).

Toxic Equivalency Factors: HED used a toxic equivalency factor (TEF) approach to sum exposure and risk estimates from thiophanate-methyl and MBC as MBC equivalents consistent with USEPA guidance (USEPA 1999). A TEF approach was used because both thiophanate-methyl and MBC share common toxicological effects (i.e., developmental and liver effects, and liver tumors), and because individuals are exposed to both compounds simultaneously on food commodities, in drinking water and on treated lawns. A non-cancer TEF is derived based on a ratio of the MBC PAD to the thiophanate-methyl PAD. Using the TEF approach, thiophanate-methyl exposure estimates were adjusted to account for the differences in toxicity endpoints between thiophanate-methyl and MBC

[1] PAD= Population Adjusted Dose = $\frac{\text{Acute or Chronic RfD}}{\text{FQPA Safety Factor}}$

(i.e., acute PAD or aPAD is 0.067 mg/kg/day for thiophanate-methyl, but 0.01 mg/kg/day for MBC, therefore a factor of 0.15 was applied to the thiophanate-methyl acute dietary estimate for females (13-50 years). For acute exposures to females of child bearing age (13-50 years), an TEF of 0.15 was used to convert thiophanate-methyl exposures into MBC equivalents. For non-cancer chronic exposures, TEFs of 0.093 and 0.93 were used to convert thiophanate-methyl exposures into MBC equivalents for females and children, and the general population, respectively. A cancer TEF value of 5.77 was used to convert the thiophanate-methyl cancer exposure estimates to MBC equivalents (i.e., thiophanate-methyl Q_1* is 5.77 times more potent than the MBC Q_1*).

Dietary Exposure and Risk: HED has conducted acute and chronic dietary risk assessments for thiophanate-methyl, and MBC and other the metabolites of concern. HED expresses dietary risk estimates as a percentage of the acute PAD (aPAD) or chronic PAD (cPAD). Dietary exposures that are less than the 100% of the aPAD or cPAD are below HED's level of concern

The acute and chronic dietary risk assessments for thiophanate-methyl and MBC and other benzimidazole metabolites (2-AB, 4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S) are based on anticipated residues (ARs) (based on maximum supported use patterns) derived primarily from field trial residue data and percent crop treated data. Monitoring data from USDA Pesticide Data Program (PDP) and the FDA Surveillance monitoring program are not available for thiophanate-methyl. Field trial residue data are considered by the Agency as an upper-end, or worst case scenario of possible thiophanate-methyl residues, and are more suited to the requirements of tolerance setting than to the requirements of dietary risk assessment. Where percent crop treated estimates indicated no thiophanate-methyl use, a default minimum assumption of 1% crop treated was applied. Where residues were nondetectable, one-half the limit of quantitation (LOQ) of 0.05 ppm was assumed for treated commodities.

The acute dietary analysis estimates risks above HED's level of concern at the 99.9th percentile of exposure for infants (< 1 year) as a result of MBC exposure from thiophanate-methyl use (108% of aPAD). The consumption of canned peaches contributes most (70%) to the risk estimate. For all other population subgroups, acute dietary risk estimates were less than 100% of the aPAD for thiophanate-methyl and MBC, and below HED's level of concern. The acute dietary risk estimates range from 9% to 21% of the acute PAD at 99.9th percentile for thiophanate-methyl, with infants (< 1 year) being the highest exposed population subgroup. For MBC, the acute dietary risk estimates range from 4% to 108%, with the highest risk estimates for infants (< 1 year). The chronic non-cancer dietary analysis indicates all risk estimates are below HED's level of concern for all population subgroups for either thiophanate-methyl or MBC. The highest chronic dietary risk estimates are 1% and 20% of the chronic PAD, for thiophanate-methyl and MBC, respectively, for the highest exposed population subgroup, children (1-6 years). The lifetime cancer risk estimates are $2x10^{-6}$ and $4x10^{-7}$ for thiophanate-methyl and MBC, respectively. Generally, HED is concerned when cancer risk estimates exceed $1x10^{-6}$ or one-in-one million.

In addition, total thiophanate-methyl and MBC dietary risks were estimated using the TEF approach because both chemicals cause similar toxic effects following oral exposure, and because simultaneous exposure is plausible for these chemicals on food commodities given the rapid degradation of thiophanate-methyl to MBC. The highest total non-cancer chronic risk estimate is 21% of the cPAD for liver/thyroid effects, for children 1-6 years. The highest acute dietary risk estimate represents 58% of the aPAD for developmental effects for females 13-50 years of age. The total **lifetime cancer**

risk estimate is 2x10^{-6}, which exceeds HED's level of concern. Overall, there are significant uncertainties in the dietary risk assessment because of an absence of reliable residue data to support several existing tolerances, and a lack of monitoring data.

Water Exposure and Risk: The available environmental fate data suggest that thiophanate-methyl rapidly degrades to MBC in the environment (i.e., <1 to 2 days in aerobic soil, and water, respectively). Therefore, both thiophanate-methyl and MBC are likely to be present in ground water or surface water following thiophante methyl use. MBC has a low potential to leach to groundwater in measurable quantities from most typical agricultural uses based on its high soil organic carbon partition coefficient (Koc) of 2,100 l/kg, respectively. MBC is less mobile, and significantly more persistent in many soils, especially under anaerobic conditions than thiophanate-methyl.

There are no drinking water monitoring data on the concentrations of thiophanate-methyl or MBC from registered thiophanate-methyl uses. Therefore, potential exposures and risks from thiophante methyl and MBC residues in drinking water were assessed using modeling techniques (Tier 1 SCI-GROW for groundwater and Tier 1 GENEEC or Tier 2 PRZM/EXAMS for surface water) provided by the Environmental Fate and Effects Division (EFED). Inputs to the models included the highest annual thiophanate-methyl use rates on ornamentals, turf, and onions at the maximum application rate. For risk assessment purposes, groundwater estimated acute and chronic environmental concentrations (EECs) range from 0.006 to 0.17 Fg/L for thiophanate-methyl and 0.51 to15 Fg/L for MBC. For thiophanate-methyl, long-term average EECs in surface water range from 0.44 to 367, while acute EECs range from 50 to 2,100 Fg/L based on the same assumptions. For MBC, long-term average EECs in surface water range from 50 to 243 Fg/L, while acute EECs range from 210 to 1,600 Fg/L. Under HED's interim approach for incorporating estimated exposures to residues of thiophanate-methyl, MBC or both in drinking water, drinking water level of comparisons (DWLOCs) are compared to EECs. When EECs are greater than the DWLOCs, HED considers the estimate of aggregate risk to exceed HED's level of concern

Residential Exposure and Risk: Most of the residential/non-occupational scenario non-cancer risk estimates exceeded HED's level of concern for both residential handlers and postapplication exposures to children and adults for thiophanate-methyl (i.e., MOE < 300), while only a few cancer risk estimates were of concern (i.e., exceeded 1x10^{-6}). Potential residential exposures are anticipated as a result of homeowner application and professional lawn care operator application. Exposures to residential handlers during mixing, loading and application to turf and postapplication exposure to residues by adults and children on treated turf, golf courses, and ornamentals were evaluated. Residential handler exposures were to thiophanate-methyl, while postapplication exposures were to thiophanate-methyl and MBC. The duration of exposure is short-term for residential handlers, and short- and intermediate-term for post application exposures. Exposure scenarios with risk estimates for thiophanate-methyl that exceed HED's level of concern (i.e., MOEs <300) are: children playing on treated lawns (MOEs of concern range from 9 to 240), spot and broadcast lawn treatment using a hose-end sprayer, low pressure handwand, belly grinder or by hand application (MOEs of concern range from 58 to 230), and picking fruit at home by an adult (MOE of concern is 210). The scenarios with MOEs above 300 for thiophanate-methyl that are not of concern are: mowing activities, golfing, some spot treatments of lawns and ornamentals with a ready-to-use hose end sprayer or backpack sprayer and broadcast lawn treatment with a push-type spreader. All postapplication risk estimates for MBC were above 1000, and therefore do not exceed HED's level of concern. Residential handler cancer risk estimates range from 5.2x10^{-9} to 3.2x10^{-6} for thiophanate-methyl, while post-application cancer risk estimates range from 1.9×10^{-8} to 3.7×10^{-6} for combined thiophanate-methyl and MBC exposures. Residential risk estimates utilized the submitted residue dissipation studies and a turf transfer study, as well as the EPA's draft (1997) and updated (2001) SOPs for Residential Exposure Assessment.

Aggregate Exposure and Risk: As mandated by the FQPA amendments to the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency must consider total aggregate exposure from food, drinking water, and residential sources of exposure to thiophanate-methyl and MBC. This aggregate assessment considers exposure to thiophanate-methyl and MBC from food, drinking water and residential uses. In addition, the Agency has concerns about possible residential risks from thiophanate-methyl spray drift. The Agency is currently developing methods to assess residential exposures and risks from spray drift, and these will be assessed in the future when new methods are available. Because both thiophanate-methyl and MBC have common acute, short-term oral and chronic toxicity endpoints (i.e., developmental effects for acute, decreased body weight and food consumption for short-term, and liver effects and liver tumors for chronic), it is appropriate to add thiophanate-methyl and MBC dietary (food and water) and residential risk estimates. In addition, because thiophanate-methyl degrades to MBC, individuals may be exposed to both residues simultaneously on a given food commodity and on treated lawns. Risk estimates were combined using the TEF approach. The **acute, short-term, intermediate-term and chronic non-cancer and cancer aggregate thiophanate-methyl and MBC risk estimates exceed HED's level of concern** for combined exposure to thiophanate-methyl and MBC through food, drinking water sources and/or residential uses.

Aggregate risk estimates for **acute (infants <1 year), short-term, intermediate-term and chronic cancer exposure durations,** exceed HED's level of concern because food exposures, and residential exposure estimates alone, exceed HED's level of concern (i.e., > 100% aPAD, > 1×10^{-6} lifetime cancer risk estimate, and residential exposures have MOEs <300 for thiophanate-methyl) under these risk assessments. As a result, the HED Drinking Water Levels of Comparison (DWLOCs) are effectively zero for the acute (infants < 1 year), short-term, intermediate-term and cancer aggregate risk assessments. For acute effects for females (13-50 years), and children (1-6 years), the estimated surface water concentrations of MBC exceed the DWLOC and HED's level of concern. However, the estimated groundwater concentrations of MBC do not exceed the DWLOC for acute effects, or HED's level of concern. Similarly, for chronic (non-cancer) effects in infants and children, the estimated surface water concentrations of MBC exceed the DWLOC and HED's level of concern, while the groundwater concentrations of MBC do not exceed the DWLOC or HED's level of concern. In conclusion, the estimated exposures to MBC (derived from thiophanate-methyl use) in surface water, when combined with dietary and residential exposure estimates, **exceed HED's level of concern** for acute, short-term, intermediate-term, and chronic cancer and non-cancer risk estimates. In some instances, acute and chronic non-cancer aggregate risk estimates for food and drinking water derived from groundwater sources do not exceed HED's level of concern. However, the modeled EECs are based on conservative assumptions regarding the application and fate and transport of thiophanate-methyl and MBC, and do not reflect dilution to source tap nor water treatment.

HED also conducted an aggregate exposure assessment for MBC resulting from registered uses of thiophanate-methyl, and MBC. Thiophanate-methyl, which degrades to MBC, is registered for residential lawn and home orchard use, and is applied to golf courses, while MBC is registered as a paint additive in residential settings.

The **aggregate** MBC exposure from all uses (thiophanate-methyl, and MBC) and thiophanate-methyl risk estimates **exceed HED's level of concern for acute, short and intermediate-term, chronic non-cancer and cancer estimates.** Dietary exposures to MBC (from thiophanate-methyl use), residential exposures to thiophanate-methyl, and exposures resulting from MBC's use as a paint additive were the most significant contributors to the aggregate risk estimates of concern.

In accordance with current OPP policy (S. Johnson 11/17/97), if the EECs exceed the DWLOCs, water monitoring data may be required to refine the drinking water exposure estimate. SRRD and EFED should determine the nature and extent of the water monitoring data required.

The Agency is in the process of formulating guidance for conducting cumulative risk assessment. When the guidance is finalized, thiophanate-methyl, MBC and other compounds with similar mechanism of toxicity will be revisited to assess the cumulative effects of exposure to multiple compounds.

Occupational Exposure and Risk: Occupational exposures to thiophanate-methyl can occur during handling, mixing, loading and application activities. Because environmental fate data suggest that the thiophanate-methyl converts to MBC, postapplication exposures were evaluated for both thiophanate-methyl and MBC residues. Occupational postapplication exposure can occur for agricultural workers during scouting, irrigation, cultivation, harvesting and handling seeds, seedlings, and seed pieces.

Based on toxicological criteria and potential for exposure, HED has conducted dermal and inhalation exposure assessments for occupational handlers exposed to thiophanate-methyl and dermal exposure assessments for occupational postapplication exposures to thiophanate-methyl and MBC. Inhalation is not expected be a significant postapplication exposure route, except for possibly handling treated seeds for planting, for which limited non- chemical-specific data are available. The duration of exposure is expected to be short-, and intermediate-term for both occupational handler, and postapplication exposures during agricultural and harvesting activities, and long-term for a few postapplication activities. The exposure duration for short-term assessments is 1 to 7 days. Intermediate-term durations are 1 week to 6 months, and long-term durations are greater than 6 months. For dermal and inhalation risk assessment, risk estimates are expressed in terms of the Margin of Exposure (MOE), which is the ratio of the NOAEL selected for the risk assessment to the exposure. For occupationally exposed workers, MOEs $100 (i.e., 10x for interspecies extrapolation and 10x for intraspecies variability) for dermal and inhalation exposures are considered to be below the Agency's level of concern.

The majority of **occupational risk estimates for handlers** exposed to thiophanate-methyl do not exceed HED's level of concern with PPE or engineering controls. HED identified 25 major handler scenarios, which when combined with the typical range of application rates resulted in 168 scenarios. The results of the short- and intermediate-term handler assessment indicate that about half of the baseline exposure scenarios (i.e., long pants, long sleeved shirts, no gloves) had MOEs $ 100; 90% of scenarios had MOEs $ 100 when maximum PPE were added (long sleeved shirt, long pants, shoes, socks, chemical-resistant gloves, and dust/mist respirator), and all MOEs were greater than

100 when engineering controls were added, if feasible. For mixing and loading wettable powder formulations to support aerial or chemigation applications, engineering controls (i.e., water-soluble packaging) are required to achieve the target MOE for many crops and use patterns. The MOEs were less than 100 for the highest application rate for loader/applicators using push-spreaders and belly grinders, and no feasible engineering controls are available. Where data for baseline exposures were available, in general risk estimates did not exceed the level of concern (*except* when application rates exceed 10 lbs ai/acres) at baseline attire for: (1) mixing and loading dry flowable formulations; (2) loading granular formulations; (3) applying with any equipment; (4) mixing/loading/applying with any equipment; and (5) flagging to support aerial applications.

Cancer risks were estimated for the various handler scenarios assuming individual or farm-based ("private") applicators would apply less frequently than professional or "commercial" operators using only the average or "typical" application rates. At baseline, most of the exposure scenarios had estimated cancer risks less than 10^{-4}, but greater than 10^{-6}. Cancer risk estimates at baseline for private and commercial handlers range from 9.4×10^{-4} to 3.1×10^{-9}, and from 9.4×10^{-3} to 9.2×10^{-9}, respectively. With the addition of PPE, cancer risk estimates for all private handler scenarios and most commercial handler scenarios were less than 10^{-4}. With PPE, cancer risk estimates for private and commercial handlers ranged from 1.2×10^{-8} to 5.5×10^{-5}, and from 1.4×10^{-8} to 5.5×10^{-4}, respectively. With the addition of engineering controls, where feasible, cancer risk estimates for all private handler scenarios were equal or less than 2.9×10^{-6}, and estimates for commercial applicators ranged from 1.1×10^{-7} to 2.9×10^{-5}. Handler scenarios with high application rates (greater than 10 lbs ai/acre), very high acreage crops (i.e., 1200 acres per day) or hand-held application equipment generally had cancer risk estimates greater than 10^{-6}, even with addition of PPE or engineering controls. Most hand application methods (hand-directed sprays, spreaders, etc.) do not have a practical means of enclosure or other engineering control. There are insufficient data to adequately assess the seedling or dip applications, and additional data are requested to support these uses. The agricultural handler assessments are believed to be reasonable representations of thiophanate-methyl uses. Surrogate data from the Pesticide Handlers Exposure Database (PHED), Occupational and Residential Exposure Task Force (ORETF), or published literature, were used to assess handler exposure because no chemical-specific studies are available.

The results of the short- and intermediate-term **dermal postapplication assessments** for workers exposed to thiophanate-methyl and MBC indicate that the MOEs were less than 100 for most tree crops, cut flowers/herbaceous ornamentals and some lawn-care activities at the current WPS-required restricted entry intervals (REIs) of 12 hours, and therefore exceed HED's level of concern. The REI represents the duration in days which must elapse before the Agency would not have a concern (MOE # 100) for a worker wearing a long-sleeved shirt and long pants to enter the treated area and perform specific tasks. The thiophanate-methyl risk estimates were considerably higher when residue data from dry (western) versus humid (eastern) climates for apple trees, or from non-irrigated turf versus irrigated turf were used to predict worker risks. The thiophanate-methyl risk estimates for tree crops generally attained an MOE of 100 within one week for most activities when NY data were used, while one to several months were required to attain an MOE of 100 when WA data were used to estimate risks for apples, peaches, grapes, and large ornamentals. High-contact activities on turf required 7 days to attain an MOE of 100 using non-irrigated turf data, but only 2 days using the irrigated turf data. Row crop reentry risk estimates using strawberry Dislodgable Foliar Residue (DFR) data indicated 1 day was sufficient to achieve an MOE of 100 for most tasks, except working with ornamentals. These risk estimates are less certain for crops which do not resemble strawberry plants in architecture and leaf surface. Cut flowers risk estimates, using data for transfer coefficients and residues from thiophanate-methyl studies, showed MOEs of 100 were not attained until 1-2 months after application. Using 14 day average residues, cancer risk estimates for most activities on most crops were between 10^{-4} and 10^{-6}, although some high-contact activities exceeded 10^{-4}, notably those involving cut flowers and woody ornamentals.

A worker post-application exposure scenario was also assessed for the metabolite of thiophanate-methyl, MBC. The same assumptions as for thiophanate-methyl were used along with the maximum MBC DFR for each study. The highest MBC DFR value was used because of the uncertainties in the percentage of thiophanate-methyl that degrades to MBC at any time in the environment, as well as the dissipation rate of MBC (which increases before decreasing after thiophanate-methyl application). The risk assessment indicates that noncancer risks to postapplication workers do not exceed the level of concern (MOE >100) from exposures to MBC residues as a degradate of thiophanate-methyl. For short-term risks, the MOEs range from 250 to 630,000 with a target of 100. Cancer risk estimates range from 4.4×10^{-6} to 1.9×10^{-8}. All of the REIs are based on MOEs using thiophanate-methyl residues alone as the highest detected MBC residues incurred an MOE of 250.

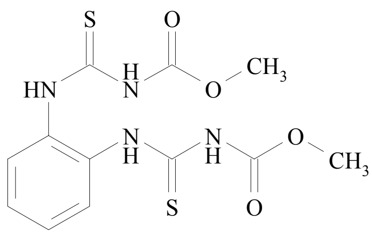
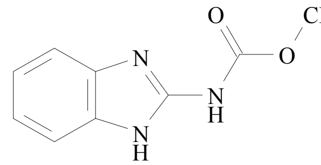
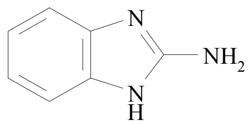
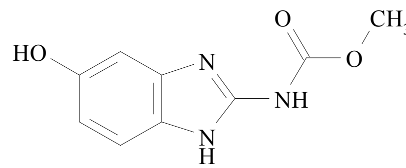
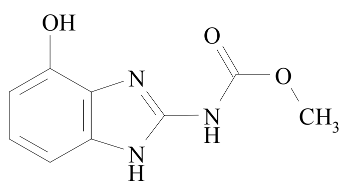
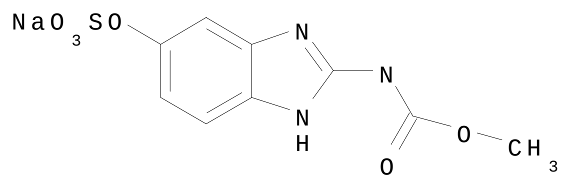
Chemical-specific postapplication exposure DFR data were submitted for apples, strawberries and turf and cut flowers. These data were used along with HED standard transfer coefficients derived using recently submitted Agricultural Re-entry Task Force (ARTF) data, to assess potential exposures to workers reentering treated sites. The occupational postapplication assessment is believed to be reasonably representative of thiophanate-methyl uses.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Thiophanate-methyl [dimethyl [(1,2-phenylene)bis(iminocarbonothioyl)] bis(carbamate)] (CAS Registry No.:23564-05-8) has an empirical formula of $C_{12}H_{14}N_4O_4S_2$, and a molecular weight of 342.4. Pure thiophanate-methyl is a colorless crystalline solid with a melting point of 168 EC with decomposition. Technical thiophanate-methyl is a pale brown powder which begins to decompose at - 163 EC. Thiophanate-methyl is slightly soluble in water (21.8 ppm) and sparingly soluble in most organic solvents at 25 EC (2.9 g/100 mL acetone; 7.8×10^{-1} g/100 mL methanol; 8.4×10^{-1} g/100 mL ethyl acetate; 7.3×10^{-2} g/100 mL dichloromethane; 1.8×10^{-2} g/100 mL n-octanol; 1.1×10^{-2} g/100 mL xylene; and 4.7×10^{-5} g/100 mL n-hexane). Thiophanate-methyl is a semi-volatile compound based on its vapor pressure of 1.3×10^{-5} mmHg.

The HED Metabolism Committee (S. Funk, 3/6/97) has concluded that the residues to be regulated in plant and animal commodities for purposes of tolerance enforcement will consist of thiophanate-methyl and its metabolite methyl 2-benzimidazolyl carbamate (MBC). For purposes of dietary risk assessment, the residues of concern in plants will include thiophanate-methyl, MBC, and 2-aminobenzimidazole (2-AB). In animal commodities, the residues of concern will include thiophanate-methyl, MBC, and the hydroxylated metabolites of MBC (4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S). The chemical names and structures of these compounds are depicted in Figure A.

Figure A. Chemical structures of thiophanate-methyl residues of concern.

 **Thiophanate-methyl; dimethyl [(1,2-phenylene)bis (iminocarbonothioyl)]bis(carbamate)**	 **MBC: methyl-2-benzimidazole carbamate**
 **2-AB: 2-amine-1H-benzimidazole**	 **5-OH-MBC: Methyl 2-(5-hydroxybenzimidazolyl) carbamate**
 **4-OH–MBC: Methyl 2-(4-hydroxybenzimidazolyl) carbamate**	 **5-OH-MBC-S: sodium 5-(2-methoxycarbonylamino) benzimidazolyl sulfate**

Thiophanate-methyl rapidly degrades to carbendazim (MBC) in surface water (i.e., less than one day). MBC is also a white solid that has a molecular weight of 191.2 and is not very soluble in water (8 mg/L at pH of 7). MBC is more stable than thiophanate-methyl, especially under aerobic conditions. MBC has a typical aerobic soil metabolism half life ($T_{½}$) of 320 days and aerobic and anaerobic aquatic metabolism half life of 61 days (Memorandum from I. Abdel-Saheb to D. Smegal, Drinking Water Assessment for Thiophanate-methyl, September 1999). The soil/water partition coefficient (K_{oc}) value for MBC is 2,100 l/kg, indicating that MBC is not very mobile in soils. MBC is not volatile based on its low vapor pressure of $1x10^{-7}$ mmHg at 20º C.

There is only one thiophanate-methyl manufacturing-use product (MP), the 97% technical (T; EPA Reg. No. 4581-280), which is registered to Elf Atochem North America. Because thiophanate-methyl is a List B chemical, only the 97% T/TGAI is subject to a reregistration eligibility decision. However, there are 36 active registrations and 22 special local need registrations. Most pertinent data requirements are satisfied for the thiophanate-methyl 97% T/TGAI; however, additional data are required concerning OPPTS 830.1550, 830.1620, 830.1670, 830.1750, and 830.6313. In addition, data are required concerning UV/visible absorption for the PAI (OPPTS 830.7050). Provided that the registrant submits the data required in the attached data summary table for the 94.3% T, and either certifies that the suppliers of beginning materials and the manufacturing process for the thiophanate-methyl TGAI have not changed since the last comprehensive product chemistry review or submits a complete updated product chemistry data package, HED has no objections to the reregistration of thiophanate-methyl with respect to product chemistry data requirements.

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile Overview

Adequacy of Toxicology Database/Data Gaps: At this time, the toxicology database for thiophanate-methyl is incomplete. The Hazard Identification Assessment Review Committee (HIARC, meeting of April 8, 1999, and September 26, 2000) requested that rat acute and subchronic neurotoxicity screening studies be submitted and that a developmental neurotoxicity study be placed in 'reserve' status pending the results of these studies and a developmental neurotoxicity study with MBC. The HIARC also requested a 90 day rat inhalation study because an unacceptable 14-day inhalation study showed possible respiratory effects from thiophanate-methyl exposure at lower concentrations than those associated with developmental effects and because occupational exposures are potentially long-term in green houses. The Cancer Assessment Review Committee (CARC, April 28, 1999 meeting) requested submission of the following additional genotoxicity studies: a preincubation *Salmonella typhimurium* mammalian microsome gene mutation assay, a mouse lymphoma L5178 cell forward gene mutation assay with colony sizing and a mouse *in vivo* bone marrow assay with antikinetochore staining. In addition, the metabolite 2-aminobenzimidazole metabolite should be tested at minimum in the *S. typhimurium* mammalian microsome gene mutation assay.

The quality of the currently available acceptable toxicity studies on thiophanate-methyl is considered high.

Toxicology data for carbendazim (Methyl 2-Benzimidazole Carbamate) or MBC, the primary environmental breakdown product of thiophanate-methyl, are also considered in this assessment. In foods and the environment, thiophanate-methyl rapidly transforms to MBC, hence environmental residues on plants and water to which people maybe exposed are primarily MBC. MBC is also registered for use as a systemic carbamate fungicide in paints in residential settings, but has no registered food uses in the US, nor import tolerances. The HIARC requested two toxicity studies with MBC, a 21 day dermal toxicity study in rats and a developmental neurotoxicity study in rats. In addition, the 2-generation rat reproduction and subchronic studies for MBC fail to meet the Subdivision F Guidelines. The available toxicology studies are summarized in Appendix A (Tables A-1 and A-2 for thiophanate-methyl and MBC, respectively).

Acute Toxicity. Both thiophanate-methyl and MBC possess a low order acute toxicity by oral, dermal and inhalation routes of exposure (categories III/IV). Thiophanate-methyl is only slightly irritating to the skin and is not an ocular irritant (both category IV), but is a dermal sensitizer. MBC is in category III for primary eye irritation. MBC is not a skin sensitizer. Acute toxicity values and categories for the technical grade of thiophanate-methyl and MBC are summarized on Tables 1 and 2, respectively.

Subchronic/Chronic Systemic Toxicity: The liver and thyroid are the primary target organs of thiophanate-methyl in several species following subchronic or chronic dietary exposure. In the Fischer-344 rat subchronic toxicity study, thyroid and liver enlargement, hepatocellular hypertrophy and thyroid hypertrophy/hyperplasia were observed, although alterations in thyroid hormone levels were not reported. In the chronic toxicity/carcinogenicity study on Fischer-344 rats, thyroid and liver were enlarged and alterations in circulating thyroid hormones [increased thyroid stimulating hormone (TSH); decreased T3/T4] were observed. Serum cholesterol was also increased. Microscopically, liver hypertrophy, lipofuscin pigmentation, focal fatty degeneration and necrosis were observed in males and hypertrophy and lipofuscin deposition in females. Thyroid hypertrophy and hyperplasia were seen in both sexes. In the beagle dog, similar thyroid and liver effects and related clinical chemistry alterations were also observed with subchronic or chronic exposure. Serum alkaline phosphatase was also increased following chronic exposure. In the 18-month CD-1 mouse carcinogenicity study, liver enlargement and hypertrophy, and enlarged thyroid and hypertrophy/hyperplasia, were also reported. However, thyroid effects were less pronounced than in the rat or dog, with enlargement and hypertrophy/hyperplasia and sporadic circulating hormone alterations observed only at high dose levels (>1000 mg/kg/day). The effects observed in the thyroid are consistent with disruption of the thyroid-pituitary homeostasis, but additional information is considered necessary to sufficiently support this mechanism.

In addition to liver and thyroid effects, thiophanate-methyl also appeared to cause mild anemia at the higher dose levels in rats, dogs and mice following subchronic or chronic exposure. In rats, thiophanate-methyl caused toxicity to the kidney and increased urinary protein (males), lipofuscin pigmentation and increased severity of nephropathy were reported following chronic administration. An increase in systemic calcification was observed in males and to a lesser extent in females and was probably secondary to hyperparathyroidism. Decreased body weight/weight gain was observed in both sexes. Male rats appeared to be more sensitive than females based on greater severity of effects and high mortality at the highest dose tested (6000 ppm or 280.6 mg/kg/day, males and 334.7 mg/kg/day, females). Beagle dogs also showed decreased body weight. In the 1 year dog study, transient tremors at the highest dose tested (HDT of 200 mg/kg/day) were also observed. In the mouse carcinogenicity study, increased heart weight (females) and incidence of atrial thrombosis were observed.

Thiophanate-methyl is a carbamate but only limited data are available on its potential to inhibit cholinesterase (ChE). As a class of compounds, thiocarbamates do not produce consistent cholinesterase inhibition patterns. In the rat subchronic toxicity study, serum cholinesterase activity was increased in males by 22-38% relative to controls but decreased in females by 25-28% at $293.2 mg/kg/day. In the rat chronic toxicity/carcinogenicity study, males showed increases in serum ChE at 280.6 mg/kg/day (HDT) at 6 and 12 months (41-42%) whereas at 24 months, it was decreased (-38%). ChE activity in females was slightly decreased (18-35%) at 6 and 12 months at $63.5 mg/kg/day. RBC and brain ChE activities were not evaluated. ChE was not measured in the subchronic or chronic dog studies.

Thiophanate-methyl administered dermally to rabbits over a period of 21 days (5 days/week, 6 hrs/day) caused decreased food consumption in females at 300 and 1000 mg/kg/day and in males at 1000 mg/kg/day. Because this decrease was reported in both sexes and a dose-response was observed in females, it is considered treatment-related although no other signs of toxicity were observed. Comparison of this dermal LOAEL with an oral LOAEL (maternal toxicity, rabbit developmental toxicity study) suggests that thiophanate-methyl is poorly absorbed into the skin. Dermal absorption was estimated at about 7% of the applied dose.

The only inhalation toxicity study submitted was a 14-day inhalation toxicity study on a formulation containing 5.2% thiophanate-methyl. Local pulmonary effects were observed at the LOAEL of 0.0151 mg/L and decreased body weights at the HDT. However, in addition to testing a formulation and not the technical a.i., this study did not evaluate all of the standard parameters (e.g., clinical chemistry, hematology, organ weights, complete gross/microscopic tissue evaluation) and therefore does not provide adequate information on toxicity via the inhalation route.

Only one subchronic oral study in dogs was available for MBC. Although classified as unacceptable, both liver and testicular effects were noted at MBC doses as low as 35-40 mg/kg/day. Chronic toxicity studies are available for MBC in rats, mice and dogs. In all species, the most sensitive toxicological endpoint is liver toxicity that occurred at levels as low as 12.5 mg/kg/day for MBC, indicating that MBC may be more toxic than thiophanate-methyl following chronic exposure. Dogs appear to be the most sensitive species for liver toxicity following chronic oral exposure to MBC.

Carcinogenicity. Thiophanate-methyl is classified as "likely to be carcinogenic to humans". Thiophanate-methyl caused a dose-related increase in the incidence of thyroid follicular cell tumors in male and female F-344 rats at the highest 2 dose levels tested ($54.4 mg/kg/day). In males, a positive increasing trend and a pair wise increase in incidence of adenomas, carcinomas and combined adenomas/carcinomas at the HDT were observed. In females, the incidence of adenomas was lower and showed a significant increasing trend but no pair wise increase. No carcinomas were observed. In both sexes, the incidence was increased above available historical control values; however, these data were not from the study lab or from the same supplier within 2-3 years of the study conduct. In CD-1 mice, statistically significant, dose-dependent increases in hepatocellular adenomas were observed in males at the highest 2 dose levels tested ($476.6 mg/kg/day) and also in females at $123 mg/kg/day. A significant increasing trend was also observed in both sexes. The combined incidence of adenoma and carcinoma was also increased in males, but the incidence of carcinomas alone was not increased. These incidences were above the available historical control values for studies from the same lab and for the same strain from the supplier, some within 2-3 years of the conduct of this study.

MBC is classified in group C (possible human carcinogens) because it induced liver tumors (hepatocellular adenoma and/or carcinomas) in mice. There is no evidence of carcinogenicity in rats for MBC. It is noted that the MBC rat studies only tested 36 rats/sex/dose (and only 20/sex/dose in the 250 mg/kg/day MBC dose group), when current guidelines require 50 rats/sex/dose.

Developmental/Reproductive Toxicity: Developmental toxicity was observed in the fetuses of rabbits exposed to 40 mg/kg/day thiophanate-methyl and included increased incidence of supernumerary ribs and decreased fetal weight. These findings occurred at a dose that also caused maternal toxicity based on decreases in body weight gain and food consumption. There were no abnormalities observed in the rat at gavage doses up to 1000 mg/kg/day or in the rat dietary developmental study as doses up to 163 mg/kg/day. Increased offspring sensitivity was not observed in the reproductive toxicity studies. In the 2-generation reproductive toxicity study, parental toxicity was observed at all doses tested ($13.7 mg/kg/day) based on mild hepatocellular hypertrophy and thyroid hypertrophy/hyperplasia, whereas offspring toxicity was observed at $43.3 mg/kg/day as slightly reduced body weights of the F2b offspring during lactation. Although the offspring NOAEL and LOAEL (8 mg/kg/day and 32 mg/kg/day, respectively) were lower than the parental systemic NOAEL and LOAEL ($32 mg/kg/day and >32 mg/kg/day, respectively) in the 3-generation reproductive toxicity study, liver and thyroid of parental animals were not evaluated and therefore the evidence for increased offspring susceptibility in that study is considered equivocal.

There is increased sensitivity of rat and rabbit fetuses as compared to maternal animals following *in utero* exposure to MBC, in prenatal developmental toxicity studies. In the MBC rat study, increased sensitivity manifested as developmental anomalies [decreased fetal body weight and increases in skeletal variations and a threshold for malformations, i.e., some malformations noted but not statistically significant) at doses of 20 mg/kg/day which were not maternally toxic. At higher doses of 90 mg/kg/day, treatment-related malformations of the central nervous system (CNS) were observed which included exencephaly, domed head, anophthalmia, microphthalmia and bulged eyes. For developmental toxicity the NOAEL was 10 mg/kg/day, whereas for maternal toxicity, the NOAEL was 20 mg/kg/day (based on a slight increase in liver weight at 90 mg/kg/day).

In the rabbit developmental study with MBC, increased sensitivity manifested as decreased implantations and litter size, and increased resorptions at 20 mg/kg/day; the NOAEL is 10 mg/kg/day. Maternal toxicity was not observed until higher doses of 125 mg/kg/day, based on abortions and decreased maternal body weight; the maternal NOAEL is 20 mg/kg/day.

MBC was associated with adverse reproductive effects (decreased birth weight at weaning) in an unacceptable reproductive toxicity study in rats. MBC also caused adverse testicular effects characterized by premature release of immature germ cells, atrophy of a few seminiferous tubules and significant decrease in seminiferous tubule diameter following a single gavage dose with 50 mg/kg (Nakai et al. 1992). In addition, evidence of testicular effects has been demonstrated in the unacceptable 90-day subchronic dog study with MBC.

Genotoxicity. Although the acceptable submitted genotoxicity studies (*in vitro* CHO cytogenetic and rat liver unscheduled DNA synthesis assays) were negative for thiophanate-methyl, two published reports (mouse bone marrow micronucleus and BALB/c 3T3 cell transformation assays) demonstrated that thiophanate-methyl is aneugenic. Weak equivocal positive results were observed in a published Ames assay. The CARC determined that additional genotoxicity testing should be provided to adequately assess direct mutagenicity of thiophanate-methyl: (1) a *Salmonella typhimurium* mammalian microsome gene mutation assay (pre-incubation modification) to resolve the equivocal results from the literature; (2) a mouse lymphoma L5178Y mammalian cell forward gene mutation assay, including colony sizing; (3) an *in vivo* mouse micronucleus assay should be performed and the Agency prefers that this assay include immunofluorescent antikinetochore-specific antibody staining. Finally, (4) the 2-aminobenzimidazole metabolite of thiophanate-methyl should be tested at minimum in the *S. typhimurium* mammalian microsome gene mutation assay because of the structural alert for mutagenesis (i.e, the NH_2 group attached to the imidazole ring).

MBC has marginal mutagenic activity in standard <u>in vitro</u> studies. In contrast, there is clear and reproducible evidence of aneuploidy (i.e., abnormal number of chromosomes) both <u>in vitro</u> and <u>in vivo</u>. There is also convincing evidence that the induction of aneuploidy by MBC is primarily attributed to adverse effects on cellular spindle apparatus. MBC is an established spindle poison that induces aneuploidy effects in both <u>in vitro</u> and <u>in vivo</u> test systems. For example, nondisjunction was reported in A. nidulans and many other test systems. MBC also produced positive effects in bone marrow antikinetochore micronucleus assays, which were consistent with a spindle effect. However, MBC is not clastogenic. Since the genotoxic activity of MBC is well known, MBC is frequently used as a test chemical (i.e., positive control) for the assessment of new assay systems for the detection of aneuploidy induction.

In mutagenicity studies with MBC, there is compelling evidence of aneuploidy induction following oral dosing in mice. Mutagenicity data support the evidence of developmental anomalies in rats and hepatocellular tumors in several strains of male and female mice.

Neurotoxicity. No acute or subchronic rodent neurotoxicity screening studies (§81-8 and §82-7) were submitted for thiophanate-methyl. The HIARC (meeting of 4/8/99) determined that these studies should be submitted based on (1) potential clinical signs of neurotoxicity in the chronic dog study (transient tremors) and (2) existence of a common metabolite, MBC, with benomyl. In an earlier HIARC meeting (memorandum from J. Rowland to B. Madden, 12/3/97; HED Doc. No. 012418), it was determined that benomyl, which has a metabolite in common with thiophanate-methyl (MBC), showed potential signs of neurotoxicity in the acute and subchronic rat neurotoxicity screening studies. In addition, in the rat developmental toxicity studies, both MBC (MRID No. 40438001) and benomyl (MRIDs 00148393, 00119017) caused developmental neurotoxic effects. Developmental neurotoxicity studies (§83-6) were therefore requested for benomyl and MBC. A developmental neurotoxicity study for thiophanate-methyl is in 'reserve' status pending the receipt/evaluation of neurotoxicity studies and development of a policy on the need for a developmental neurotoxicity study for pesticides that cause thyroid toxicity. The Agency has concern for potential effects on the development of the nervous system if thiophanate-methyl has antithyroid activity.

MBC does not appear to cause delayed neurotoxicity in hens. Developmental CNS malformations were noted in the MBC prenatal developmental toxicity study in rats, which included exencephaly, domed head, anophthalmia, microophthalmia and bulged eyes.

Metabolism/Pharmacokinetic Studies. There was no significant retention of thiophanate-methyl or its metabolites in tissues and most of the administered dose was excreted within 24 hrs post-dosing. The extent of metabolism of parent compound and amount of radioactivity excreted in the urine and feces was greatest following a single oral low dose compared to a single oral high dose or repeated low dosing.

In the rat, MBC is excreted primarily in the urine with lesser amounts excreted in the feces, and MBC is poorly distributed to the tissues. MBC was rapidly absorbed and extensively metabolized in CD/BR rats following single oral doses up to 1000 mg/kg. The half-life of MBC was approximately 12 hours, and 98% of MBC was excreted by 72 hours post-administration. The primary reactions involved in the metabolism of MBC were oxidation of the phenyl ring, followed by conjugation to yield sulfate and glucoronide conjugates of 5-hydroxycarbendazim and 5,6-dihydroxycarbendazim. Subsequent phenyl ring oxidation and N-oxidation at the imidazole nitrogen led to significant levels of 5,6-hydroxy-oxo-carbendazim N-oxide glucuronide conjugate, especially in female rats.

Dermal Absorption. HED estimated a dermal absorption rate of 7% based on the results of an oral developmental toxicity study (LOAEL of 20 mg/kg/day) and a 21-day dermal toxicity study (LOAEL of 300 mg/kg/day) in the same species (rabbit) with similar endpoints (decreased food consumption). HED estimated a dermal absorption rate of 3.5% for MBC based on a dermal absorption study with benomyl. Benomyl was selected as a surrogate chemical because of similarities in toxicological effects and structure between benomyl and MBC.

Mechanism of Action. In order to characterize the mechanism of thyroid tumorigenesis, a series of short-term studies were undertaken to determine whether thiophanate-methyl had antithyroid activity. These studies demonstrated that thiophanate-methyl caused liver and thyroid enlargement, increased circulating TSH and decreased T3/T4 after 2 to 8 days' treatment with thiophanate-methyl at 6000 ppm (equivalent to the HDT in the rat chronic toxicity/carcinogenicity study). Some liver microsomal enzymes, including UDP-glucuronosyltransferase, were increased. The effects on liver and thyroid weight were reversible, but reversibility of the alterations in circulating hormone levels and on microscopic effects were not evaluated. Supplementation of treated animals with T4 prevented thyroid enlargement and increased TSH but did not prevent liver enlargement. Thiophanate-methyl also appeared to have a mild inhibitory effect on microsomal thyroid peroxidase. These data were reviewed by the HED CARC. Although it was determined that the available evidence is consistent with disruption of thyroid-pituitary homeostasis by thiophanate-methyl, additional data were considered necessary to adequately support this mechanism. The current Agency policy on rat thyroid tumors (US EPA, 1998) requires demonstration of the reversibility of the thyroid hormonal alterations and microscopic changes after withdrawal of treatment; these data demonstrated only reversibility of thyroid weight. In addition, there were insufficient genotoxicity data for evaluation of direct mutagenicity of thiophanate-methyl.

Other metabolites. The primary metabolites of MBC are 5-hydroxy-2-benzimidazolecarbamic acid, methyl ester (5-HBC) and 2-aminobenzimidazole (2-AB). The acute toxicity of 5-HBC and 2-AB could not be compared to MBC since they were not tested at levels higher than 3400 and 7500 mg/kg, respectively. MBC did not cause death in rats following single oral doses of 5000 mg/kg. Deaths (6/6) occurred with 2-AB following 10 doses at 670 mg/kg/day (2/6 occurred with MBC at 3400 mg/kg/day). 5-HBC was not tested higher than 200 mg/kg/day for 10 doses over 2 weeks. Testicular degeneration was observed with 5-HBC at 3400 mg/kg but not with 2-AB up to 7500 mg/kg.

Table 1
Acute Toxicity of Thiophanate-methyl

Guideline No.	Study Type	MRID #	Results	Toxicity Category
870.1100 (81-1)	Acute Oral, Rat	41644301	LD_{50} = >5000 mg/kg,	IV
870.1200 (81-2)	Acute Dermal, Rabbit	41644302	LD_{50} = >2000 mg/kg,	III
870.1300 (81-3)	Acute Inhalation, Rat	41482804	LC_{50} >1.7 mg/L males LC_{50} >1.9 mg/L females	III
870.2400 (81-4)	Primary Eye Irritation, Rabbit	40095501	slight ocular irritant	IV

Guideline No.	Study Type	MRID #	Results	Toxicity Category
870.2500 (81-5)	Primary Skin Irritation, Rabbit	40095502	Non-irritant	IV
870.2600 (81-6)	Dermal Sensitization, Guinea Pig	41482805	dermal sensitizer	N/A

N/A Not applicable

Table 2
Acute Toxicity of MBC

Guideline No.	Study Type	% a.i.	MRID or Accession No.	Results	Toxicity Category
870.1100 (81-1)	Acute Oral, Rat	98	256025 (Acc No)	LD_{50} = >10,000 mg/kg,	IV
870.1200 (81-2)	Acute Dermal, Rabbits	75 INE 965	256025 (Acc No)	LD_{50} = >2,000 mg/kg formulation	III
870.1300 (81-3)	Acute Inhalation, Rat	75 INE 965	256025 (Acc No)	LC_{50} >5 mg/L	IV
870.2400 (81-4)	Primary Eye Irritation, Rabbit	>98	256025 (Acc No)	minimal to no irritation	III
870.2500 (81-5)	Primary Skin Irritation, Rabbit	75 INE 965	256025 (Acc No)	slight irritation at 24 hr, normal by 72 hr	IV
870.2600 (81-6)	Dermal Sensitization, Guinea Pig	98	256025 (Acc No)	not a dermal sensitizer	N/A
870.6100a (81-7)	Delayed neurotoxicity, hen	Not given	241931 (Acc No)	NOAEL = 2500 mg/kg	N/A

N/A Not applicable

3.2 FQPA Considerations

The HED FQPA Safety Factor Committee met on October 16, 2000 to re-evaluate the hazard and exposure data for thiophanate-methyl and recommended that the FQPA safety factor (as required by the Food Quality Protection Act of August 3, 1996) should be reduced to 3x in assessing the risk posed by thiophanate-methyl. In June 7, 1999, the HED FQPA Safety Factor Committee (SFC) met to evaluate the hazard and exposure data for benomyl and carbendazim or MBC, the primary metabolite of both benomyl and thiophanate-methyl, and recommended that the FQPA safety factor should be retained at 10x in assessing the risk posed by both benomyl and MBC. FQPA SFC concluded (See memo from B. Tarplee October 25, 2000 HED Doc No. 014363) that the FQPA safety factor is necessary but can be reduced to **3X for thiophanate-methyl** because:

- the toxicity database is incomplete (acute and subchronic neurotoxicity studies are required due to evidence of neurotoxicity) and the requirement for a developmental neurotoxicity study has been ‘reserved’;

< the HIARC evaluated the new 1997 prenatal developmental toxicity study in rabbits and classified this study as Acceptable for assessment of susceptibility;

< the HIARC agreed with the HED ToxSAC that the dietary prenatal developmental toxicity study in the rat was considered to be Acceptable for assessment of susceptibility;

< the HIARC concluded that the available data provided no indication of increased susceptibility *in utero* exposure in the developmental studies in rats and rabbits or following pre-/postnatal exposure in the multi-generation reproduction studies in rats; and

< the dietary (food and drinking water) and non-dietary exposure assessments will not underestimate the potential exposures for infants and children from the use of thiophanate-methyl.

The Committee determined that **3X FQPA** safety factor for thiophanate-methyl is applicable to **all population subgroups for dietary and non-dietary exposure assessments of all durations** since the toxicology database for thiophanate-methyl is incomplete and the requirement for a developmental neurotoxicity study has been ‘reserved’.

The FQPA SFC concluded (See memo from B. Tarplee July 1, 1999 HED Doc No. 013544) that the FQPA safety factor be retained at **10X for carbendazim or MBC**, the primary metabolite of thiophanate-methyl, because of:

< evidence of increased susceptibility following *in utero* exposure of carbendazim, the primary metabolite of thiophanate-methyl, in the prenatal developmental toxicity study in rats and rabbits; and

< the need for developmental neurotoxicity study in rats for carbendazim.

The Committee determined that **10X FQPA** safety factor for carbendazim, is applicable for the following subpopulations:

< Females 13-50 since increased susceptibility was demonstrated following *in utero* exposure and

< Infants, Children (1 - 6 years), and Children (7 - 12 years) due to the uncertainty resulting from data gaps for the developmental neurotoxicity study in rats for carbendazim or MBC.

The Committee determined that 10X FQPA safety factor for carbendazim is applicable for the following risk assessment scenarios:

< all risk assessments (acute/chronic dietary and residential scenarios for all durations) since increased susceptibility was seen following *in utero* exposure (which could occur after a single dose) and since there is uncertainty resulting from the need for developmental neurotoxicity study in rats. This study may provide data that could be used in the toxicology endpoint selection for dietary and nondietary exposure risk assessments.

3.3 Dose-Response Assessment

3.3.1 Non-Cancer Endpoints

On September 26, 2000, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to reassess the acute and chronic dietary, and dermal and inhalation endpoints for risk assessment for thiophanate-methyl, and its primary metabolite carbendazim (MBC), respectively. The Committees decisions for thiophanate-methyl are presented in the HIARC memorandum dated November 6, 2000 (J. Doherty to S. Knizner, HED Doc. No.014370). The Committees decisions for MBC are presented in the HIARC memorandum dated March 2001 (D. Smegal to C. Eiden). To assess dietary exposure, HIARC developed acute and chronic RfDs for both thiophanate-methyl and its primary metabolite, MBC, based on exposure concerns. Because thiophanate-methyl and MBC cause developmental effects, HIARC developed two acute dietary RfDs (aRfD) for each compound, one for females of the child bearing age (13-50 years) and one for the general population, including infants and children.

Thiophanate-methyl

For thiophanate-methyl, HIARC identified aRfDs of 0.2 mg/kg/day and 0.4 mg/kg/day for females 13-50 years and the general population, respectively. The aRfD for females (13-50 years) is based on a NOAEL of 20 mg/kg/day from a 1997 rabbit developmental study that observed an increased incidence of supernumerary ribs in fetuses of pregnant rats administered 40 mg/kg/day (LOAEL). The thiophanate-methyl aRfD for the general population is based on a NOAEL of 40 mg/kg/day for tremors observed in 7 of 8 dogs, 2-4 hours following a single dose of 200 mg/kg (LOAEL). The cRfD is 0.08 mg/kg/day based on a NOAEL of 8 mg/kg/day for thyroid effects and decreased body weight in dogs chronically given 40 mg/kg/day. An uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variability) was applied to the NOAELs to obtain the RfDs.

For short- and intermediate-term incidental oral ingestion and inhalation exposures, HIARC selected the oral NOAEL of 10 mg/kg/day from the 1997 rabbit developmental study based on decreased maternal body weight and food consumption at 20 mg/kg/day (LOAEL) for use in risk assessment. The short- and intermediate-term dermal endpoints are based on a dermal NOAEL of 100 mg/kg/day from a 21-day dermal study in rabbits that observed decreased body weight and food consumption at 300 mg/kg/day (LOAEL). The long-term dermal and inhalation endpoints are based on the NOAEL of 8 mg/kg/day for thyroid effects and decreased body weight in the chronic dog study. Because an oral NOAEL was selected for all inhalation endpoints and the long-term dermal endpoint, a 100% inhalation absorption factor (i.e., equivalent to oral absorption), and a 7 percent dermal absorption factor were applied to these endpoints, respectively. The dermal absorption rate of 7% was estimated based on the results of an oral developmental toxicity study and a 21-day dermal toxicity study in the same species (rabbit) with similar endpoints (decreased food consumption).

MBC

The acute dietary RfDs for MBC are 0.1 mg/kg/day and 0.17 mg/kg/day for females (13-50 years) and the general population, respectively. The aRfD for females (13-50 years) is based on a NOAEL of 10 mg/kg/day from a rat developmental study in which decreased fetal body weight, increases in skeletal variations and a threshold for malformations were observed at 20 mg/kg/day (LOAEL). The aRfD for the general population is based on a LOAEL of 50 mg/kg/day for effects on the male reproductive system [sloughing (premature release) of immature germ cells 2 days post exposure, atrophy of a few seminiferous tubules in one testicle, significant decrease in seminiferous tubule diameter, and slight abnormal growth of the efferent ductules at 70 days post exposure]. This effect was seen at the lowest dose tested, therefore, a NOAEL could not be established for the aRfD for the general population. The cRfD of 0.025 mg/kg/day is based on an oral NOAEL of 2.5 mg/kg/day from a 2-year dog study in which histopathological lesions of the liver and chronic hepatitis in both sexes were observed at 12.5 mg/kg/day (LOAEL). An uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variability) was applied to the NOAELs to obtain the RfDs, except for the aRfD for the general population, which has a total uncertainty factor of 300 (extra factor of 3X) to account for the absence of a NOAEL.

For short-term incidental oral ingestion exposures, HIARC selected an oral NOAEL of 10 mg/kg/day from the 1997 rabbit developmental study with thiophanate-methyl based on decreased maternal body weight and food consumption at 20 mg/kg/day (LOAEL) for use in risk assessment. Thiophanate-methyl was selected as a surrogate because there is no appropriate endpoint for infants and children in the MBC database. The intermediate-term incidental oral endpoint is based on adverse liver effects in the 90 day dog study with MBC. For MBC, HIARC identified short- and intermediate term dermal NOAELs of 10 mg/kg/day from a rat developmental study that observed adverse fetal effects at 20 mg/kg/day (LOAEL) for females 13-50 years. The long-term dermal NOAEL is 2.5 mg/kg/day from a 2-year dog study that observed liver toxicity at 12.5 mg/kg/day (LOAEL). Because oral NOAELs were selected, a 3.5 percent dermal absorption factor, based on a rat dermal absorption study with benomyl was used.

Due to an absence of inhalation data for MBC, the inhalation NOAEL of 0.96 mg/kg/day for benomyl based on respiratory effects was also used to assess inhalation exposures for MBC for all durations.

Population Adjusted Doses

The Population Adjusted Dose (PAD) is the term that OPP is now using to describe a reference dose (RfD) – either acute or chronic– that has been adjusted to take into account the FQPA Safety Factor. PAD (acute or chronic) = RfD (acute or chronic) ÷ FQPA Safety Factor. These PADs are referred to as aPAD and cPAD, respectively.

Depending on the determinations of the HED FQPA SFC, the FQPA safety factor may be the same or different for acute and chronic risk assessments, and may apply to either designated or all population subgroups. For thiophanate-methyl, the FQPA safety factor was reduced to 3X, and was applied to all population subgroups for all exposure assessments. For MBC, the FQPA safety factor of 10 was retained for both acute and chronic risk assessments, and applies to the following subgroups: females (13-50 years), all infants, children (1 - 6 years), and children (7 - 12 years). The doses and toxicological endpoints selected for various exposure scenarios and subgroups for thiophanate-methyl and MBC are summarized in Tables 3 and 4, respectively.

3.3.2 Classification of Carcinogenic Potential

Thiophanate-methyl was classified as a "likely to be carcinogenic to humans" by the HED Cancer Assessment Review Committee (CARC) on April 28, 1999. A Q_1^* of 1.38×10^{-2} $(mg/kg/day)^{-1}$ was assigned based on the dose-dependent increases in liver tumors in male and female mice (quantitative risk assessment memorandum from L. Brunsman to N. McCarroll dated March 16, 2000). The thyroid tumors in rats were also considered treatment-related because a dose-dependent increase was observed in both sexes (in males, toxicity at the HDT was excessive based on high mortality but the tumors were nonetheless considered treatment-related). Although evidence supporting a threshold mechanism for thyroid tumor induction based on disruption of thyroid-pituitary homeostasis was submitted, the CARC determined that additional information (e.g., demonstration of reversibility of treatment-induced thyroid hormonal alterations and morphological changes after cessation of treatment, additional genotoxicity studies) was required to adequately demonstrate this mechanism. Special mechanistic studies submitted in support of this mechanism are described in the toxicity chapter (memo from D. Smegal/L. Hansen to D. Scher, March 15, 2001, D272850).

MBC was classified as group C (possible human carcinogens) by the HED Cancer Peer Review Committee, and on 5/21/86, the Scientific Advisory Panel (SAP) concurred with this classification of MBC. The rationale for this classification is as follows: (1) the carcinogenic response for MBC is confined solely to the mouse liver, even with repeated experiments; (2) the liver tumors produced by MBC were observed in 2 related strains of mice (CD-1 and Swiss SPF) known to have high background incidence rates of liver tumors, whereas no liver tumors were produced by MBC in another strain of mice [NMRKf (SPF 71)] known to have a low background incidence rate of liver tumors; (3) MBC produced weak mutagenic effects consistent with spindle poison activity rather than gene mutation or DNA repair activity.

The Cancer Peer Review Committee noted the occurrence of mostly malignant hepatocellular tumor response with MBC in two stains of mice, and the presence of unusually occurring and malignant hepatoblastomas with MBC in male SPF Swiss mice. In addition, the mutagenicity information indicates that the aneuploidy known to be produced by MBC could theoretically result in a loss of tumor suppressor genes and a potential oncogenic effect.

HED estimated a unit risk Q_1* of 2.39×10^{-3} $(mg/kg/day)^{-1}$ for MBC (memorandum from L. Brunsman to D. Smegal, November 18, 1999, HED Doc no 013859). This estimate is based on the outcome of the re-evaluation of the hepatocellular (adenoma and/or carcinoma) tumors in CD-1 female mice with dose levels of 0, 500, 1500 or 7500 ppm MBC (Wood et al. 1982). The Q_1* was estimated using the $(mg/kg/day)^{3/4}$ species scaling factor. Details of the quantitative estimate are presented in the Toxicity Memorandum..

Table 3 Summary of Doses and Toxicological Endpoints for Thiophanate-methyl			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF* and Endpoint for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary, Females 13-50 yrs	NOAEL=20 mg/kg/day UF = 100 **Acute RfD=** 0.2 mg/kg/day	FQPA SF = 3 **aPAD**= acute RfD / FQPA SF = 0.067 mg/kg/day	1997 Rabbit Developmental Study LOAEL=40 mg/kg/day based on supernumerary ribs in fetuses of exposed dams.
Acute Dietary, General Population	NOAEL=40 mg/kg/day UF = 100 **Acute RfD=** 0.4 mg/kg/day	FQPA SF = 3 **aPAD**= acute RfD / FQPA SF = 0.13 mg/kg/day	Chronic oral toxicity dog study LOAEL= 200 mg/kg/day based on tremors 2-4 hours post-dosing in 7 of 8 dogs.
Chronic Dietary	NOAEL=8 mg/kg/day UF = 100 **Chronic RfD=** 0.08 mg/kg/day	FQPA SF = 3 **cPAD**= chronic RfD / FQPA SF = 0.027 mg/kg/day	Chronic oral toxicity dog study LOAEL= 40 mg/kg/day based on thyroid effects and decreased body weight.
Short-and Intermediate Term Incidental Ingestion	Oral NOAEL =10 mg/kg/day	**LOC for MOE = 300** for all residential populations **LOC for MOE = 100** for occupational workers	1997 Rabbit Developmental Study LOAEL= 20 mg/kg/day based on decreased maternal body weight and food consumption.
Short- and Intermediate-Term Dermal	Dermal NOAEL = 100	**LOC for MOE = 300** for all residential populations **LOC for MOE = 100** for occupational workers	21-Day Rabbit Dermal Toxicity Study LOAEL = 300 mg/kg/day based on decreased body weight (28%) and food consumption (15%).
Short-and Intermediate Term Inhalation (a)	Oral NOAEL =10 mg/kg/day (inhalation absorption rate=100% relative to oral absorption)	**LOC for MOE = 300** for all residential populations **LOC for MOE = 100** for occupational workers	1997 Rabbit Developmental Study LOAEL= 20 mg/kg/day based on decreased maternal body weight and food consumption.
Long-Term Dermal and Inhalation (a)	NOAEL=8 mg/kg/day (dermal absorption rate =7% relative to oral absorption; inhalation absorption rate=100% relative to oral absorption)	**LOC for MOE = 300** for all residential populations **LOC for MOE = 100** for occupational workers	Chronic oral toxicity dog study LOAEL= 40 mg/kg/day based on thyroid effects and decreased body weight.
Cancer (a)	$Q1^* = 1.38 \times 10^{-2}$ $(mg/kg/day)^{-1}$ (dermal absorption rate =7% relative to oral absorption; inhalation absorption rate=100% relative to oral absorption)	$Q1^* = 1.38 \times 10^{-2}$ $(mg/kg/day)^{-1}$	78-week mouse study based on male mouse liver adenoma and/or carcinoma and/or hepatoblastoma combined tumor rates

* The reference to the FQPA Safety Factor refers to any additional safety factor retained due to concerns unique to the

FQPA.
UF = Uncertainty Factor
PAD = Population Adjusted Dose (includes UF and FQPA safety factor)
LOC= Level of Concern
MOE = Margin of Exposure
(a) Since an oral value was selected, 7% dermal absorption factor and 100% inhalation absorption factor (equivalent to oral absorption) should be used for route-to-route extrapolation.

Table 4
Summary of Doses and Toxicological Endpoints for MBC

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary, Females 13-50 years	NOAEL=10 mg/kg/day UF = 100 **Acute RfD=** 0.1 mg/kg/day	FQPA SF = 10 **aPAD**= acute RfD / FQPA SF = 0.01 mg/kg/day	Rat Developmental Study with MBC LOAEL= 20 mg/kg/day based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations in fetuses of exposed dams
Acute Dietary, General Population, including infants and children	LOAEL=50 mg/kg/day UF = 300 **Acute RfD=** 0.17 mg/kg/day	FQPA SF = 10 for infants and children FQPA SF=1 general pop. **aPAD**= acute RfD / FQPA SF = 0.017 mg/kg/day (infants and children) = 0.17 (general pop.)	Single Dose Rat Study (Nakai et al. 1992) LOAEL= 50 mg/kg/day based on adverse testicular effects including sloughing (premature release) of immature germ cells 2 days post exposure, atrophy of a few seminiferous tubules in one testicle, significant decrease in seminiferous tubule diameter, and slight abnormal growth of the efferent ductules at 70 days post exposure.
Chronic Dietary	NOAEL=2.5 mg/kg/day UF = 100 **Chronic RfD=** 0.025 mg/kg/day	FQPA SF = 10 for children and females 13-50 yrs FQPA SF=1 general pop. **cPAD**= chronic RfD / FQPA SF = 0.0025 mg/kg/day (children and females) = 0.025 (general pop.)	2 year dog study with MBC LOAEL= 12.5 mg/kg/day based on histopathological lesions of the liver characterized as swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis in both sexes.
Short-Term Incidental Ingestion	Oral NOAEL =10 mg/kg/day	**LOC for MOE = 300** for all residential populations **LOC for MOE = 100** for occupational workers	1997 Rabbit Developmental Study with thiophanate-methyl LOAEL= 20 mg/kg/day based on decreased maternal body weight and food consumption.
Intermediate-Term Incidental Ingestion	Oral NOAEL =11 mg/kg/day (rounded to10 mg/kg/day)	**LOC for MOE = 300** for all residential populations **LOC for MOE = 100** for occupational workers	90 day dog feeding study with MBC LOAEL= 35 mg/kg/day based on adverse liver effects.

Table 4 Summary of Doses and Toxicological Endpoints for MBC			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF* and Endpoint for Risk Assessment**	**Study and Toxicological Effects**
Short-and Intermediate Term Dermal (a)	Oral NOAEL =10 mg/kg/day (dermal absorption rate = 3.5% relative to oral absorption)	**LOC for MOE = 1000** for children and females (residential) **LOC for MOE = 100** for occupational workers	Rat Developmental Study with MBC LOAEL= 20 mg/kg/day based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations in fetuses of exposed dams
Long-Term Dermal (a)	Oral NOAEL =2.5 mg/kg/day (dermal absorption rate = 3.5% relative to oral absorption)	**LOC for MOE = 1000** for children and females (residential) **LOC for MOE = 100** for occupational workers	2 year dog study with MBC LOAEL= 12.5 mg/kg/day based on histopathological lesions of the liver characterized as swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis in both sexes of dogs.
Short-, Intermediate- and Long Term Inhalation	Inhalation NOAEL= 0.96 (10 mg/m^3)	**LOC for MOE = 1000** for children and females (residential) **LOC for MOE = 100** for occupational workers	90 day rat inhalation study with benomyl LOAEL= 4.8 mg/kg/day (50 mg/m^3)based on Olfactory degeneration in the nasal cavity
Cancer (a)	Q1* = 2.39×10^{-3} $(mg/kg/day)^{-1}$ (dermal absorption rate =3.5% relative to oral absorption; inhalation absorption rate=100% relative to oral absorption)	Q1* = 2.39×10^{-3} $(mg/kg/day)^{-1}$	2 year mouse study with MBC based on hepatocellular (adenoma and/or carcinoma) tumors in female CD-1 mice

* The reference to the FQPA Safety Factor refers to any additional safety factor retained due to concerns unique to the FQPA.
UF = Uncertainty Factor
PAD = Population Adjusted Dose (includes UF and FQPA safety factor)
LOC= Level of Concern
MOE = Margin of Exposure
(a) Since an oral value was selected, 3.5% dermal absorption factor should be used for route-to-route extrapolation.

3.3.3 Toxic Equivalency Factors

In this assessment, risk estimates for thiophanate-methyl and MBC + other metabolites of concern were added together to account for total risk estimates for target organs of concern. This is considered appropriate because both chemicals have aPADs that are based on the similar developmental effects for females, identical endpoints for short-term incidental oral exposures, and the liver is a target organ of chronic exposure. In addition, individuals may be exposed to both thiophanate-methyl and MBC residues simultaneously on a given food commodity, and following lawn treatment since thiophanate-methyl rapidly degrades to MBC in the environment. A toxic equivalency factor (TEF) approach was used to sum risk estimates from thiophanate-methyl and MBC as MBC equivalents consistent with USEPA (1999) guidance. Using the TEF approach, all thiophanate-methyl dietary exposure estimates were adjusted upwards to account for differences in aPADs and cPADs between thiophanate-methyl and MBC. A TEF was not estimated for the aPADs for the general population because the target organs are different for thiophanate-methyl (tremors) and MBC (testicular effects), nor for short- and intermediate-term dermal exposures. The TEFs were estimated for the cPADs because both thiophanate-methyl and MBC cause adverse liver effects following chronic exposure. The TEFs used in this assessment are shown on Table 5 below.

Table 5
Toxic Equivalency Factors (TEFs) Used to Convert Thiophanate-methyl Exposures into MBC Equivalents

Toxicological Endpoint/ Population Subgroup	PAD or NOAEL		Toxic equivalency Factor (a)
	Thiophante Methyl (mg/kg/day)	MBC (mg/kg/day)	
Acute PAD, females 13-50 years	0.067	0.01	0.15
Acute PAD, general population	0.13	0.17	Not relevant (b)
Short-term incidental oral	10	10	1
Intermediate-term incidental oral	10	10	Not relevant (b)
Short- and intermediate-term dermal	100 (dermal study)	10 (oral study)	Not relevant (b)
Chronic PAD, females, infants and children	0.027	0.0025	0.093
Chronic PAD, general population		0.025	0.93
Cancer (Q_1*)	1.38×10^{-2}	2.39×10^{-3}	5.77

(a) MBC PAD divided by thiophanate-methyl PAD. For cancer, thiophanate-methyl Q1* divided by MBC Q1*.
(b) A TEF was not calculated because the toxicity endpoints are different. Therefore, aggregate thiophanate-methyl and MBC exposures were not combined.

3.4 Endocrine Disrupter Effects

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the

Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, thiophanate-methyl and MBC may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

4.1 Summary of Registered Uses

Thiophanate-methyl [dimethyl [(1,2-phenylene)bis(iminocarbonothioyl)]bis(carbamate)] is a systemic fungicide registered for use on vegetables, fruits, soybeans, nuts, and wheat, and on ornamental plantings. There are approximately 54 tolerances for food and/or feed commodities. Thiophanate-methyl is manufactured by Nippon Soda Company Ltd of Japan, under the trade name Topsin M®. The registrants are Elf-Atochem North America Agrichemicals, NISSO TM LLC, and Gowan Pacific LLC. Thiophanate-methyl formulations registered for use on food/feed crops include dust (D), granular (G), wettable powder (WP), water-disperable granular (WDG), and flowable concentrate (FlC) formulations. The dust formulation may be applied to potato seed-pieces at planting and the granular formulation may be applied as an in-furrow application to beans at planting. The remaining products may be applied as an in-furrow application at planting to onions (WP and WDG) or as postemergence broadcast applications to all other labeled crops using ground or aerial equipment.

The following uses are being supported by Elf Atochem: almonds; apples; bananas; beans, dry; beans, lima and snap; cucurbits; onions; peanuts; pecans; soybeans; apricots; cherries; nectarines; peaches; plums and prunes; strawberries; sugar beets; fall seeded wheat; potatoes (seed treatment only). The registrant stated that the following uses will not be supported: celery; post harvest uses on all commodities; and sugarcane.

BEAD estimates that the annual total domestic usage of thiophanate-methyl is approximately 454,000 lbs ai for over 750,000 acres treated [F. Hernandez, Quantitative Usage Assessment (QUA) memo dated November 9, 2000]. BEAD estimates thiophanate-methyl has the largest agricultural market in terms of total pounds ai allocated to soybeans (24%), sugar beets (17%), wheat (11%), dry beans (10%), apples (9%), almonds (8%), and peaches (6%). BEAD estimates that most of the usage is in AR, CA, ID, LA, ND, MN and MS, while the registrant believes most usage is in CA, ID, LA, ND, MN, PA, VA and FL. Crops with a high percentage of their total U.S. planted acres treated (i.e., percent crop treated) include peaches (26%), strawberries (21%), apples (14%), sugar beets (12%), almonds (11%), apricots (10%), nectarines (10%) plums (7%) and pecans (6%). Crops with less than one percent crop treated include peanuts, soybeans and wheat.

Comprehensive lists of thiophanate-methyl end-use products (EPs) and of use patterns with food/feed uses which are subject to re-registration are summarized in the Revised Product and Residue Chapter (Memorandum from J. Morales to D. Smegal, March 15, 2001; D272013).

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

As noted previously, thiophanate-methyl is registered on a wide variety of food crops and has approximately 54 tolerances on food and/or feed commodities. Tolerances for thiophanate-methyl residues in/on plant and livestock raw agricultural commodities (RACs) are currently expressed in terms of thiophanate-methyl, its oxygen analogue [dimethyl-4,4'-o-phenylene bis(allophanate)], and its benzimidazole-containing metabolites, (calculated as thiophanate-methyl) [40 CFR§ 180.371]. However, the HED Metabolism Committee (S. Funk, 3/6/97) concluded that the residues to be regulated in plant and animal commodities for purposes of tolerance enforcement consist of thiophanate-methyl and its metabolite methyl 2-benzimidazolyl carbamate (MBC). The tolerance definition listed under 40 CFR §180.371 should be changed to reflect the decision of the Metabolism Committee. The conclusions specified in the "Tolerance Reassessment Summary" section of the Revised Product and Residue Chemistry Chapter Memorandum from J. Morales to D. Smegal, March 15, 2001; D272013) reflect this decision.

Adequate plant and animal metabolism data are available for reregistration and risk assessment purposes. However, storage stability data are required to support the residue data for plant and animal commodities. The registrant has submitted storage stability data for animal commodities and these data are currently under review by HED. Residue data are unavailable to support many of the existing tolerances, and the residue data that are available for reassessing tolerances require supporting storage stability data.

The Codex Alimentarius Commission has established maximum residue limits (MRLs) for thiophanate-methyl residues in/on various plant and animal commodities (see *Guide to Codex Maximum Limits For Pesticide Residues, Part A.1, 1995*). Codex MRLs for thiophanate-methyl are currently expressed as carbendazim (MBC). The Codex MRL residue definition and the U.S. tolerance definition are currently incompatible and will remain incompatible even after the U.S. tolerance definition is revised, as the revised tolerance definition will include both thiophanate-methyl and MBC.

Plant Metabolism. The qualitative nature of the residue in plants is adequately understood based on adequate apple, lima bean, sugar beet, and wheat metabolism studies. The HED Metabolism Committee (S. Funk, 3/6/97) concluded that the residues of concern for dietary risk assessment in plants include thiophanate-methyl and its metabolites MBC and 2-AB. For purposes of tolerance enforcement, the regulated residues consist of thiophanate-methyl and MBC. For dietary risk assessment, 2-AB was included with the parent and MBC. Concentrations of 2-AB in plant commodities were estimated using the ratio of 2-AB to thiophanate-methyl or MBC in the various plant commodities from the metabolism studies along with residue data for thiophanate-methyl and MBC.

Animal Metabolism. The qualitative nature of the residue in animals is understood based upon adequate ruminant and poultry metabolism studies. The HED Metabolism Committee (S. Funk, 3/6/97) concluded that the residues of concern in animal commodities include thiophanate-methyl, MBC, and the hydroxylated derivatives of MBC (4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S). For purposes of tolerance enforcement, the regulated residues consist of thiophanate-methyl and MBC. For dietary risk assessment, the hydroxylated MBC metabolites were included along with the parent and MBC. Concentrations of 4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S in animal commodities were estimated using the ratio of these metabolites to thiophanate-methyl or MBC in the animal commodities from the metabolism studies along with residue data for thiophanate-methyl and MBC.

Residue Analytical Methods - Plants and Animals.

Adequate analytical methodology is available for collecting residue data on thiophanate-methyl and its metabolites (MBC, 2-AB and the hydroxylated metabolites of MBC) in plant and animal commodities; however, the requirement for acceptable enforcement methods for plant and animal RACs remains outstanding.

Methods for determination of residues in/on plant commodities: A single enforcement method for determining parent and MBC in plant commodities is listed in the Pesticide Analytical Manual (PAM), Vol. II, as Method I. As this method is a spectrophotometric method, it is no longer considered acceptable for enforcing tolerances. The two additional methods listed in PAM Vol. II, Methods A and B, are also spectrophotometric methods for plant commodities. In addition, Method A is for determining the metabolite allophanate, which is no longer a residue of concern.

The registrant has proposed a HPLC/UV detection method (Elf Atochem Method No. BR-011-04) for enforcing tolerances for thiophanate-methyl residues in/on plant commodities. In its review of this method (DP Barcodes D214622 and D215191, S. Funk, 6/8/95), the Agency concluded that the method was inadequate, but that it could be upgraded if the registrant adequately addressed the deficiencies noted in the review. The registrant, Elf Atochem, has submitted (1996; MRID 43986601) a revised version of the proposed HPLC/UV enforcement method (Method BR-93-28), along with a letter (1996, MRID 43986600) discussing the revisions and the deficiencies previously noted by the Agency. Upon review of the revised method, HED has concluded the following: a) the deficiencies previously cited by the Agency in the proposed HPLC/UV enforcement method (BR-93-28) for determining residues of thiophanate-methyl and MBC in plant commodities have been resolved. Method BR-93-28 is adequate for determining residues of TM and MBC in/on plant commodities and has a limit of quantitation (LOQ) of 0.05 ppm for each analyte; and b) HPLC/UV Method BR-93-28 must still be radio validated using samples from a plant metabolism study and undergo a successful independent laboratory validation (ILV) prior to being validated by the Agency. The registrant has submitted an independent method validation for method BR-93-28 (MRID 44703602). This independent method validation is currently under review by HED.

Data from analysis of thiophanate-methyl residues in plants have been collected using versions of the proposed enforcement method. Except for minor changes in clean-up procedures and solvent systems, these methods are essentially the same as the proposed enforcement method.

Methods for determination of residues in/on animal commodities: As noted previously, there is no currently acceptable analytical enforcement method for thiophanate-methyl. The registrant must propose an enforcement analytical method for determining residues of concern in animal commodities, validate the method using samples from the animal metabolism studies, and subject the method to an independent laboratory validation and Agency validation. The registrant has submitted an independent method validation for animal commodities and an independent method validation

(MRID 44526101). These submissions are currently under review by HED.

Data on residues of thiophanate-methyl, MBC, 4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S in milk and tissues from the ruminant feeding study were collected using adequate HPLC/UV methods that are modified versions of the above methods for plants. These methods involve extraction of residues into acidic methanol (following acid hydrolysis for milk and kidneys), solvent partitioning, and, if necessary, column clean-up prior to determining residues by reverse-phase HPLC with UV detection. The limit of quantitation for each analyte is 0.05 ppm.

Multiresidue methods: The FDA PESTDATA database indicates that thiophanate-methyl and MBC are completely recovered using FDA Multiresidue Protocol A (PAM I Section 242.2). Additional multiresidue method (MRM) recovery data are required for thiophanate-methyl and MBC through FDA MRM protocols A through G.

Storage Stability. Requirements for storage stability data are not satisfied for purposes of reregistration. To support the residue data for plant commodities, data are required depicting the frozen storage stability of thiophanate-methyl and MBC in representative raw and processed plant commodities held in frozen storage for up to 5 years; interim 2-year data should be submitted. The requested storage stability study was begun by the registrant in 2/97.

Acceptable interim (36 months) storage stability data are available indicating that thiophanate-methyl and MBC are stable in apples, cucumbers, lettuce, wheat, carrots, snap beans, spinach, sugar beet roots, tomatoes, and wheat grain stored at -20 EC for up to 3 years.

Data are also required depicting the stability of thiophanate-methyl, MBC, 4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S in representative animal commodities held in frozen storage for intervals equivalent to the maximum storage intervals in the ruminant feeding study (milk - 250 days, tissues - 225 days). Elf Atochem submitted storage stability data for thiophanate-methyl and MBC in animal commodities (MRID 44592301, 44643502) and these studies are under review by HED

Storage stability data for poultry are adequate and indicate that residues of TM, MBC, and 5'-OH-MBC are stable in eggs under frozen conditions for up to 10 months. Residues of 5'-OH-MBC and either TM or MBC are stable in poultry liver or muscle, respectively, for up to 8.5 months. These data adequately support the frozen storage intervals for poultry commodities reflected in the feeding study.

Magnitude of the Residue in Plants. Provided issues pertaining to storage stability of the residues are adequately resolved, reregistration requirements for magnitude of the residue in plants are fulfilled for the following crops/commodities: apple, cherry, onions (dry bulb), plums (fresh prunes), strawberry, and wheat grain. Adequate field trial data depicting residues of thiophanate-methyl and MBC following applications made according to the maximum or proposed federally registered use patterns have been submitted for these commodities. Geographical representation is adequate and a sufficient number of trials reflecting representative formulation classes were conducted.

In addition, reregistration requirements for residue studies on beans (dry and succulent) and peaches/nectarines are fulfilled pending label amendments for application rates and post-harvest intervals (PHIs), and storage stability data.

For purposes of reregistration, residue data are required on almonds, apricots, dried peas, cucurbit vegetables, peanuts, pecans, potatoes, soybeans, sugar beets, and wheat forage, hay, and straw. Residue data are also required on green onions unless the registrant does not intend to support this use, in which case, the label directions should be modified to restrict the use only to bulb onions and garlic. Elf Atochem submitted residue studies for the following commodities: dried peas, watermelon, squash, cucumbers, peanuts, pecans, potatoes, soybeans, and sugar beets. These studies are under review by HED.

Pending Petitions. PP# 5F4550/6H5734: Elf Atochem North America has submitted petitions for establishing tolerances for thiophanate-methyl residues in/on grapes at 5 ppm and in/on pears at 7 ppm. These petitions are currently in reject status (CBTS Nos. 16281, 16282, 166602, 16603, 16604, 16611; DP Barcodes D209958, F. Griffith, 2/2/96). Although several of the deficiencies cited in this review have since been resolved, deficiencies pertaining to following areas must still be resolved: i) amending the proposed use directions for pears, ii) independent laboratory validation of the proposed analytical enforcement method, iii) multiresidue method testing data, iv) supporting storage stability data, and v) three additional field trials for grapes. Additional grape trials have been submitted to the Agency, and are under review by HED.

<u>Magnitude of the Residue in Processed Food/Feed</u>. Provided issues pertaining to storage stability of the residues are resolved, reregistration requirements for magnitude of the residue in processed food/feed commodities are fulfilled for apple, plums, and wheat. In addition, an adequate grape processing study is available from a pending petition for a tolerance on residues in/on grapes. The requirements for processing studies on peanuts, potatoes, soybeans, and sugar beets remain outstanding. Processing studies have been submitted for the following commodities: peanut (MRID 44850901), potato (44498502), soybean (44572702), and sugar beets (44584601) and these studies are under review by HED.

Based on the available processing studies, tolerances are not required for residues in processed commodities of apples, grapes, plums, and wheat. Residues did not concentrate in apple juice, grape juice, raisins, and prunes processed from RACs bearing detectable residues. Residues concentrated slightly in wet apple pomace, but not enough to warrant establishing a separate tolerance; two separate analyses of wet pomace indicated that residues concentrated by 1x and 1.4x (1.2x average). For wheat, residues of both thiophanate-methyl and MBC were nondetectable (<0.05 ppm) in/on the wheat grain from two tests in which wheat plants were treated at - 11x the label rate (the maximum theoretical concentration factor for processed wheat fractions is 8.3x for wheat shorts); therefore, a wheat processing study was not conducted.

<u>Magnitude of the Residue in Meat, Milk, Poultry, and Eggs</u>. Tolerances have been established for thiophanate-methyl residues in ruminant (cattle, goats, and sheep) commodities at 0.1 ppm (negligible or N) in fat, meat, and meat-by-products (exc. liver and kidney), 2.5 ppm in liver, 0.2 ppm in kidney, and 1.0 ppm in milk [40 CFR §180.371]. Tolerances have also been established for thiophanate-methyl residues in hog and horse commodities at 0.1 ppm (N) in fat, meat, and meat-byproducts (exc. liver) and 1.0 ppm in liver. For poultry commodities, tolerances have been established at 0.1 ppm (N) in fat, meat, and meat-by-products (exc. liver), 0.2 ppm (N) in liver, and 0.1 ppm (N) in eggs.

Provided that the registrant submits adequate supporting storage stability data for the residues of concern in animal commodities, an adequate ruminant feeding study is available reflecting the dosing of dairy cattle for 28 days at levels equivalent to 67.1, 205, and 839 ppm in the diet (approximately 3.6x, 11x and 45x the theoretical dietary burden for beef cattle).

Based upon the results of this study and the LOQs of thiophanate-methyl (0.05 ppm) and MBC (0.05 ppm, thiophanate-methyl equivalents) in milk and tissues, tolerances for residues in milk and in fat, meat, and meat-by-products of cattle, goats, horses, and sheep should be reassessed to 0.15 ppm.

Considering the maximum theoretical dietary burden for swine (0.09 ppm) and the results of the ruminant feeding study, the Agency also concludes that a 40 CFR §180.6(a)(3) situation exists with respect to thiophanate-methyl residues in hog commodities. Therefore, tolerances for residues in hog commodities should be revoked.

Confined Accumulation in Rotational Crops. Adequate data have been submitted characterizing ^{14}C-residues in rotated lettuce, carrots, and wheat; metabolism in these rotational crops is similar to the metabolism in the primary crops. Parent, thiophanate-methyl, levels were <0.01 ppm in all crops. Thiophanate-methyl residues of concern (MBC and 2-AB) were found at levels of >0.01 ppm in lettuce from 30- and 120-day plant-back intervals and in wheat from 30- and 365-day plant-back intervals, indicating that limited rotational field trials are required. Thiophanate-methyl residues of concern (MBC and 2-AB) were found at levels of <0.01 ppm in carrot from 30- and 120-day plant-back intervals. In the confined rotation crop studies, [^{14}C]thiophanate-methyl was applied to the soil at 1.4 lb ai/A, which was the stated 1x the maximum single application rate. However, the maximum single application rate for onions is higher (11.2 lb ai/A) as is the seasonal application rates for several crops (i.e. beans - 2.8 lb ai/A/season).

Field Accumulation in Rotational Crops. As residues of concern (MBC and 2-AB) were detected at >0.01 ppm in lettuce and wheat from 30- to 365-day plant-back intervals in the confined rotational crop study, limited field rotational crop studies are required. Limited field studies should be conducted at two separate test sites using a representative root and tuber vegetable, leafy vegetable, and small grain crop at each site. In accordance with the guidance provided in OPPTS GLN 860.1900, the rotational crops should be planted at the desired rotational crop interval following the maximum number of applications of thiophanate-methyl at the maximum label rate. Residues of thiophanate-methyl and MBC should be determined in the appropriate RACs from each rotational crop.

4.2.2 Food Exposure

As noted previously, thiophanate-methyl is registered for use on a wide variety of food crops, and has approximately 54 tolerances for food and/or feed commodities. Tolerances have been established for thiophanate-methyl residues in plant (almonds, cucumbers, melons, and squash) commodities at 0.1 ppm; apricots, cherries, nectarines, peaches, peanuts, plums, prunes, and sugar beets at 15 ppm for pre and post harvest; apples at 7 ppm; strawberries at 5 ppm; bananas at 2 ppm; and beans and soybeans at 0.2 ppm [40 CFR §180.371].

Tolerances have been established for thiophanate-methyl residues in ruminant (cattle, goats, and sheep) commodities at 0.1 ppm (N) in fat, meat, and meat-by-products (excluding liver and kidney), 2.5 ppm in liver, 0.2 ppm in kidney, and 1.0 ppm in milk [40 CFR §180.371]. Tolerances have also been established for thiophanate-methyl residues in hog and horse commodities at 0.1 ppm (N) in fat, meat, and meat-by-products (excluding liver) and 1.0 ppm in liver. For poultry commodities, tolerances have been established at 0.1 ppm (N) in fat, meat, and meat-by-products (exc.liver), 0.2 ppm (N) in liver, and 0.1 ppm (N) in eggs.

The acute and chronic dietary exposure assessments were conducted using the Dietary Exposure and Evaluation Model (DEEM™) system. DEEM™ , developed by Novigen Sciences, Inc., calculates acute and chronic dietary exposure estimates to residues in food for the U.S. general population and various population subgroups. The software contains food consumption data from the USDA Continuing Survey of Food Intake by Individuals (CFSII) from 1989-1992. For chronic dietary risk assessments, the 3-day average of the consumption data for each subpopulation is combined with average residues in commodities to determine the average exposure in mg/kg/day. For acute dietary risk assessment, the entire distribution of single day food consumption events is combined with a distribution of residues in a probabilistic analysis (referred to as a "Monte Carlo" analysis) to obtain a distribution of exposures in mg/kg/day.

Dietary assessments were separately performed for thiophanate-methyl and the sum of the metabolites MBC and 2-AB for plant commodities, and thiophanate-methyl and sum of the metabolites of concern (MBC, 4-OH-MBC, 5-OH-MBC and 5-OH-MBC-S) in livestock commodities. Assessments were performed for acute, and noncancer and cancer chronic exposures. For commodities assessed using field trial data, actual residue data for thiophanate-methyl and the individual metabolites (i.e., MBC and 2-AB) were used to estimate exposures (i.e., ratio of 2-AB:TM or 2-AB:MBC). For animal commodities, the ratios of hydroxylated metabolites to MBC or thiophanate-methyl in various commodities were based on livestock studies. Details of the dietary assessment are provided in memo from S. Piper to D. Scher/D. Smegal, D272944, March, 2001.

Anticipated residues (ARs) (based on maximum supported use patterns) used in dietary risk assessment are calculated using field trial residue data, which are submitted by the registrant, and percent crop treated data [Biological Economic Analysis Division (BEAD) Quantitative Usage Analysis for thiophanate-methyl dated 11/9/2000]. Monitoring data from USDA Pesticide Data Program (PDP) and the FDA's surveillance monitoring program, although considered more reflective of actual residues are on consumed foods, are not available for thiophanate-methyl. Field trial residue data are considered by the Agency as an upper-end, or worst case scenario of possible residues, and are more suited to the requirements of tolerance setting than to the requirements of dietary risk assessment. Field trial results result in residues expected when fields are treated at the maximum rates, and do not necessarily reflect residues at the time of food consumption.

Percent crop treated data were available for almonds, apples, apricots, dry beans, green beans, bananas, cherries, cucumbers, melons (cantaloupe, and honeydew), nectarines, peaches, peanuts, pecans, plums, pumpkins, soybeans, squash, strawberries, sugar beets, watermelons, and wheat. These data were used for the acute and chronic dietary assessments. Potatoes, and onions were assumed to have 100% crop treated. Where percent crop treated estimates indicated no thiophanate-methyl use, a default minimum assumption of 1% crop treated was applied. Where residues were nondetectable, one-half the limit of quantitation (LOQ 0.05 ppm) was assumed for treated commodities.

Surrogate field trial data from similar crops were used, if necessary, to assess crops without field trial data. Examples include: onions used as a surrogate to assess green onions; watermelon data used to assess pumpkins, bitter melon and winter melon; and while plum data used to assess apricots.

Thiophanate-methyl residues may be either concentrated or reduced by activities such as drying (dried fruits), processing (juice, catsup, etc.), washing, peeling, and cooking. All available default processing factors from DEEM software, except apples (juice), potatoes, plums (prunes) and soybeans were incorporated into the dietary exposure analysis. The requirements for processing studies on peanuts, and sugar beets remain outstanding, but recent processing study submissions for peanuts, potatoes, soybeans and sugar beets are under review by HED. These processing factors are used together with the anticipated residue estimates in or on the associated RAC to estimate the residue in various processed fractions.

HED expresses dietary risk estimates as a percentage of the acute and chronic population adjusted dose (PAD). The PAD is the adjusted RfD reflecting the retention or reduction of the FQPA safety factor for all populations. The PAD is the Reference Dose (RfD), which is derived from an exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control, along with the application of uncertainty factors. The percent of the PAD is calculated as the ratio of the exposure value to the PAD (exposure/PAD x 100 = % PAD). As shown on Table 3, for thiophanate-methyl there are two PADs pertaining to acute dietary exposure and one PAD for chronic exposure. For MBC, there are three PADs pertaining to acute dietary exposure and two PADs for chronic exposure, as shown on Table 4. Exposures less than 100% of the PAD do not exceed HED's level of concern. For this analysis, it was assumed that the metabolites 2-AB, 5-OH-MBC, 4-OH-MBC and 5-OH-MBC-S have the same toxicity as MBC.

In addition, cancer risks were estimated using a cancer unit risk estimate of 1.38×10^{-2} $(mg/kg/day)^{-1}$ for thiophanate-methyl and 2.39×10^{-3} $(mg/kg/day)^{-1}$ for MBC and other metabolites of concern. Cancer risks are calculated by multiplying the 70 year exposure estimate for the U.S. population by the Q_1^*, and are expressed as a probability of developing cancer.

4.2.2.1 Acute Dietary

A refined, Tier 3 acute probabilistic dietary exposure analysis was conducted for thiophanate-methyl, incorporating maximum percent crop treated estimates from the Biological and Economic Analysis Division (BEAD), and field trial data.

Exposure (consumption x residues) was compared to the appropriate acute population adjusted dose shown previously on Tables 3 and 4 and listed in the footnotes of Table 6. As noted previously, there are a total of five aPADs, two for thiophanate-methyl and three for MBC. The aPADs for thiophanate-methyl differ based on the toxicological endpoint of concern (i.e., developmental effects for females, and tremors for the general population). A FQPA safety factor of 3X is applied to these populations. The aPADs for MBC also differ by toxicological endpoint (i.e., developmental effects for females and testicular effects for the general population). A FQPA safety factor of 10X is applied to females (13-50 years) and children subpopulations, but a FQPA safety factor of 1X is applied to all other population subgroups. The acute dietary risk analysis estimates the distribution of single day exposures for the overall U.S. population and certain subgroups. The analysis evaluates exposure to the chemical for each food commodity.

Table 6 summarizes the acute probabilistic dietary risk estimates for the U.S. Population and the most highly exposed subpopulations. For infants (< 1 year), HED's exposure estimates at the 99.9th percentile of exposure for MBC (from thiophanate-methyl use) is greater than 100% of the aPAD (108%), and therefore, exceeds HED's level of concern. For the U.S. population and all other subpopulations, exposure estimates for either thiophanate-methyl and MBC + other metabolites of concern are less than 100% of the aPADs, and therefore, are not of concern. While thiophanate-methyl dietary exposure is higher for children, the aPAD for females is lower than the aPAD for children, resulting in a higher risk estimate. Canned peaches are a major contributor (70% of the MBC risk estimates) for infants.

In addition, risk estimates for thiophanate-methyl and MBC and other metabolites of concern were added together for females (13-50 years) to account for total risk estimates for developmental effects. This is considered appropriate because both chemicals have aPADs that are based on developmental effects for females, and because individuals may consume both residues simultaneously on a given food commodity. The dietary risks for thiophanate-methyl and MBC were not combined for children or the general population because the aPADs are based on different effects (i.e., tremors for thiophanate-methyl, and testicular effects for MBC). A toxic equivalency factor (TEF) approach was used to sum dietary risk estimates from thiophanate-methyl and MBC as MBC equivalents consistent with USEPA guidance (USEPA 1999). Using the TEF approach, all thiophanate-methyl dietary exposure estimates were adjusted downwards to account for the differences in aPADs between thiophanate-methyl and MBC (i.e., aPAD is 0.067 mg/kg/day for thiophanate-methyl, but 0.01 mg/kg/day for MBC, therefore a factor of 0.15 was applied to the thiophanate-methyl dietary estimate). As shown on Table 6, this approach is identical to summing the %aPADs for thiophanate-methyl and the %aPAD for MBC. The total dietary risk estimate for thiophanate-methyl and MBC is 57.6% and is below HED's level of concern for females (13-50 years).

Table 6. Summary of Thiophanate-methyl/MBC Acute Dietary Probabilistic Exposure Analysis (Tier 3) by DEEM (99.9th Percentile of Exposure)

Population (a)	Thiophanate-methyl Estimate		MBC+other metabolites Estimate (from Thiophanate-methyl)		Thiophanate-methyl and MBC	Total Risk Estimate for Thiophanate-methyl and MBC
	Exposure (mg/kg/day) (b)	% aPAD (c)	Exposure (mg/kg/day) (b)	% aPAD (c)	Total Exposure in MBC Equivalents (mg/kg/day) (d)	% aPAD (e)
U.S. Population	0.011375	8.6	0.006838	4	NA	NA
All Infants <1 year	0.02847	21.4	0.018429	108	NA	NA
Children 1-6 years	0.021471	16.1	0.013911	81.8	NA	NA
Children 7-12 years	0.01379	10.4	0.008852	52	NA	NA
Females 13-50	0.006729	10	0.004756	47.6	0.00576	57.6

NA= Not appropriate due to different toxicological endpoints for TM and MBC.

(a) In addition to the U.S. population -all seasons, the most highly exposed subgroup within each of the infants, children, and females is listed.
(b) 99.9th percentile of exposure.
(c) Percent of aPAD = (Exposure ÷ aPAD) x 100%. aPAD for the general population = 0.13 and 0.17 mg/kg/day for TM and MBC, respectively, aPAD for females (13-50) = 0.067 and 0.01 mg/kg/day for TM and MBC, respectively and aPAD for children subgroups = 0.13 and 0.017 mg/kg/day for TM and MBC, respectively.
(d) Thiophanate-methyl dietary exposure adjusted using the toxic equivalency factor (TEF) of 0.15 for females 13-50 years to account for the differences in the aPADs for TM and MBC. Example, TM exposure = 0.006729 mg/kg/day * 0.15 = 0.001 mg/kg/day (in MBC equivalents) + 0.004756 = 0.00576 mg/kg/day.
(e) Percent of MBC aPAD = (Total exposure in MBC equivalents ÷ aPAD for MBC) x 100%. This is also equivalent to: %aPAD from TM + %aPAD from MBC. This is considered appropriate because the aPADs are based on developmental effects for females 13-50 years.

The uncertainties in the acute dietary exposure estimates are discussed below following the chronic dietary exposure assessment discussion.

4.2.2.2 Chronic Cancer and Non-Cancer Dietary

A refined Tier 3 chronic exposure analysis was performed using the DEEM TM exposure modeling software. The input values for the Tier 3 analyses included average residues from field trials and incorporated average percent of the crop treated information from BEAD. As noted previously, there is one cPAD for thiophanate-methyl and two cPADs for MBC. These cPADs were presented previously on Tables 3 and 4, and are shown in the footnotes of Table 7. Exposure was compared to the relevant cPAD for each chemical and subpopulation. A summary of the residue information included in this analysis can be found in the attached memorandums from S. Piper to D. Scher/D.Smegal, March, 2001, D272944.

As shown in Table 7, non-cancer chronic risk estimates for all population subgroups are below the Agency's level of concern (<100% cPAD). The most highly exposed population subgroups are children (1-6 years) for MBC and other metabolites of concern at 20% of the cPAD, and infants (1 year) for thiophanate-methyl at 1.2% of the cPAD. Similar to the acute dietary risks, a total dietary risk estimate was calculated, because of similar adverse effects, and the potential for simultaneous exposure to these chemicals on food commodities. A TEF approach was used to sum dietary risk estimates from thiophanate-methyl and MBC as MBC equivalents. Using the TEF approach, the thiophanate-methyl dietary exposure estimates for the general population and children were adjusted downwards to account for the differences in cPADs between thiophanate-methyl and MBC (i.e., general population cPAD is 0.027 mg/kg/day for thiophanate-methyl, but 0.025 mg/kg/day for MBC, therefore a factor of 0.93 was applied to the thiophanate-methyl dietary estimate). For females and children, the dietary exposure estimates were adjusted downwards using a TEF of 0.093 to account for the difference in the cPADs (i.e., 0.027 mg/kg/day for thiophanate-methyl and 0.0025 mg/kg/day for MBC). As shown on Table 7, this approach is identical to summing the %cPADs for thiophanate-methyl and the %cPAD for MBC. As shown on Table 7, the highest total dietary risk estimate of 21% for children 1-6 years, was also well below the cPADs, and therefore, does not exceed HED's level of concern.

Table 7 also presents the lifetime (70 year) cancer risk estimates for the U.S. general population. The cancer risk estimates are 1.51×10^{-6} and 3.89×10^{-7} for thiophanate-methyl and MBC, respectively. The total dietary cancer risk estimate is 2×10^{-6}. These lifetime risk estimates exceed the level the

Agency generally considers to be negligible for excess lifetime cancer risk (i.e., 1×10^{-6}). It is appropriate to add the cancer risk estimates from thiophanate-methyl and MBC because both chemicals cause mouse liver tumors, and because both chemicals are found concurrently on food items treated with thiophanate-methyl.

Uncertainties of Dietary Exposure Estimates

The Agency believes that the Tier 3 risk assessment presented is the most refined to date for acute dietary exposure to thiophanate-methyl and MBC. However, there are some uncertainties associated with this exposure estimate as follows. Overall, HED considers the risk estimates to be conservative, representing high-end exposures, because of the data used and approach taken.

(a) The consumption database used in the dietary exposure analysis (CSFII, 1989-1992) has a limited number of individuals in the age group infants less than one year old. The USDA is currently conducting the Supplemental Children's Survey (approximately 5000 children).

(b) Residues potentially present at the time of consumption are not represented in this analyses. This is because the dietary exposure analyses relied primarily on field trial data. Additionally, percent crop treated data were not available for some commodities (potatoes and onions) and 100% crop treated was assumed.

(c) Relative amounts of thiophanate-methyl and MBC were determined from plant metabolism studies. Because thiophanate-methyl degrades to MBC, over time more MBC and less thiophanate-methyl may be present in food at the time of consumption. In addition, for the acute dietary assessment, it may be conservative to add the 99.9th percentile exposure estimates for thiophanate-methyl and MBC, because as thiophanate-methyl residues decline, MBC residues increase. Consequently, individuals could be exposed to high-end (i.e., 99.9th) residues of either thiophanate-methyl <u>or</u> MBC, not both at the same time. This uncertainty only affects the total acute dietary risk estimates for females (13-50 years), because the thiophanate-methyl and MBC dietary risk estimates for children were not combined due to lack of common toxicological endpoints.

(d) Data reflecting possible reduction of residues by washing or peeling commodities are not available. These data may lead to lower dietary exposure estimates.

(e) No cooking factors could be incorporated in this dietary exposure analysis. If Elf-Atochem has any such data they should be supplied to the Agency. If reduction of residues is noted upon cooking, this could lead to lower acute dietary exposure estimates.

(f) Canned peaches contribute 70% of the MBC risk estimates for infants (which is 108% of the aPAD). The peach dietary exposure estimate is based on field trial data, where thiophanate-methyl was applied at 65% of the label maximum application rate of 1.6 lb ai/A (i.e., applied at 1.05 lb ai/A). It is possible that these data could underestimate dietary exposures to peaches treated at the maximum application rate.

(g) In the absence of adequate toxicity data for the metabolites 2-aminobenzimidazole (2-AB) 5-OH-MBC, 4-OH-MBC and 5-OH-MBC-S it was assumed that all four metabolites are toxicologically equivalent to MBC on a gram basis.

(h) Data from four plant metabolism studies (apple, sugar beets, wheat and lima beans) were used to extrapolate to all other registered plant uses to estimate the ratio of thiophanate-methyl:MBC residues.

Table 7 Summary of Thiophanate-methyl and MBC Tier 3 Chronic Dietary Exposure Analysis by DEEM									
Population Subgroup (a)	**Thiophanate-methyl**			**MBC +other metabolites (from Thiophanate-methyl)**			**Thiophanate-methyl and MBC**	**Total Risk for Thiophanate-methyl and MBC**	
	Exposure (mg/kg BW/day)	**%cPAD (b)**	**Lifetime Cancer Risk Estimate (d)**	**Exposure (mg/kg BW/day)**	**%cPAD (b)**	**Lifetime Cancer Risk Estimate (d)**	**Total Exposure in MBC Equivalents (mg/kg/day) (e)**	**%cPAD (c)**	**Lifetime Cancer Risk Estimate (f)**
US Population	0.000109	0.4	$1.51 x 10^{-6}$	0.000163	0.7	$3.89 x 10^{-7}$	0.000264 (non cancer) 0.000792 (cancer)	1.1	$2 x 10^{-6}$
All infants (< 1 yr)	0.000329	1.2	NA	0.000343	13.7	NA	0.000373	15	NA
Children (1-6 years)	0.000262	1	NA	0.000501	20	NA	0.000526	21	NA
Children (7-12 years)	0.000171	0.6	NA	0.000294	11.8	NA	0.00031	12	NA
Females 13-50	0.000075	0.3	NA	0.00012	4.8	NA	0.000127	5.1	NA
Males (13-19 yrs)	0.000079	0.3	NA	0.000175	7	NA	0.000248	1	NA

NA = Not applicable, these groups are included in the 70 year U.S. population estimate

(a) In addition to the U.S. population -all seasons, the most highly exposed subgroup within each of the infants, children, females, and males groups is listed.

(b) Percent of cPAD = (Exposure ÷ cPAD) x 100%. cPAD for thiophanate-methyl = 0.027 mg/kg/day. cPAD for MBC= 0.025, 0.0025 and 0.0025 mg/kg/day for the general population, females 13-50 yrs and children, respectively.

(c) Percent of MBC cPAD = (Total exposure in MBC equivalents ÷ cPAD for MBC) x 100%. This is also equivalent to the sum of the %cPAD for thiophanate-methyl and MBC+2-AB. This is considered appropriate because the cPADs are based on the same adverse effect (liver) for thiophanate-methyl and MBC.

(d) Lifetime cancer risk = Exposure x Q1*.

(e) Thiophanate-methyl dietary exposure adjusted using the toxic equivalency factors (TEFs) of 0.093 for females and children, and by a TEF of 0.93 for the general population to account for the differences in the cPADs for thiophanate-methyl and MBC. Example, thiophanate-methyl exposure = 0.000109 mg/kg/day * 0.93 = 0.0001 mg/kg/day in MBC equivalents + 0.000163 = 0.000264 mg/kg/day. For cancer, a TEF of 5.77 was applied to the thiophanate-methyl dietary exposure to estimate MBC equivalents.

(f) Total lifetime cancer risk estimate is the sum of thiophanate-methyl and MBC cancer risks. Both chemicals cause mouse liver tumors.

4.3 Drinking Water Exposure/Risk Pathway

The Agency currently lacks sufficient water-related exposure data from monitoring to complete a quantitative drinking water exposure analysis and risk assessment for thiophanate-methyl and MBC. Therefore, the Agency is presently relying on water-quality models to estimate environmental concentrations (EECs) of pesticides in ground and surface water to estimate drinking water exposures to thiophanate-methyl and MBC. Generic Estimated Environmental Concentrations (GENEEC) and/or the Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS) (both product estimates of pesticide concentration in a farm pond) predict EECs for pesticides in surface water. The Screening Concentration in Ground Water (SCI-GROW) (an empirical model based on actual monitoring data collected for a number of pesticides that serve as benchmarks) predicts EECs for pesticides in ground water. These models take into account the use patterns and environmental profile of a pesticide, but do not include consideration of the impact that processing raw water for distribution as drinking water may have on the removal of pesticides from the source water. The primary use of these models by the Agency at this stage is to provide a coarse screen for assessing whether a pesticide is likely to be present in drinking water at concentrations that would exceed human health levels of concern.

The SCI-GROW model generates a single EEC value of pesticide concentrations in ground water. That EEC is used to assess drinking water exposures in assessments of both acute and chronic dietary risk. It is not unusual for the ground water EEC to be significantly lower than the surface water EECs. The GENEEC model generates several time-based EEC values of pesticide concentration in surface water, ranging from 0-days (peak) to 56-days (average). The GENEEC peak (maximum)EEC is used in assessments of acute dietary risk; the GENEEC 56-day (average) EEC is used in assessments of chronic (non-cancer and cancer) dietary risk. PRZM/EXAMS provides longer duration values (up to a 36-year mean) of pesticide concentrations in surface water, and is mainly used when a refined EEC is needed.

A drinking water level of comparison (DWLOC) is the concentration of a pesticide in drinking water that would result in risk estimates below HED's level of concern, when considering total aggregate exposure to that pesticide from food, water, and residential uses. HED uses DWLOCs in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. DWLOC values are not regulatory standards for drinking water, however, they do have an indirect regulatory impact through aggregate exposure and risk assessment. In the absence of monitoring data for a pesticide, the DWLOC is used as a point of comparison against the conservative EECs provided by computer modeling (SCI-GROW, GENEEC, PRZM/EXAMS). A DWLOC may vary with drinking water consumption patterns and body weights for specific subpopulations.

HED back-calculates DWLOCs by a two-step process: exposure [food + (if applicable) residential exposure] is subtracted from the PAD to obtain the maximum exposure allowed in drinking water; DWLOCs are then calculated using that value and HED default body weight and drinking water consumption figures. In assessing human health risk, DWLOCs are compared to EECs. When EECs are **greater** than DWLOCs, HED considers the aggregate risk [from food + water + (if applicable) residential exposures] to exceed HED's level of concern.

4.3.1 Environmental Profile

The Environmental Fate and Effects Division (EFED) provided EECs for thiophanate-methyl and its primary degradate, MBC, based on Tier 1 modeling (using GENEEC, and SCI-GROW) and Tier 2 modeling (PRZM/EXAMS) (Attached memos from R. Pisigan/I. Abdel-Saheb, January 19, 2001, and April 11, 2001). The available environmental fate data suggest that thiophanate-methyl rapidly degrades to MBC following application to ornamentals, turf and agricultural crops. MBC has a low potential to leach to groundwater in measurable quantities from most typical uses based on its high soil organic carbon partition coefficient (Koc) of 2,100 l/kg. The available data indicate that the primary metabolite of thiophanate-methyl, MBC, is less mobile and significantly more persistent in many soils, especially under anaerobic conditions. The MBC aerobic soil half-life is 320 days, while the aerobic and anaerobic aquatic metabolism half-lives are 61 and 743 days, respectively. EFED concludes that MBC will probably not reach ground water to any significant concentration due to its high Koc. EFED (EFED; memo by R. Pisigan/I. Abdel-Saheb, January 19, 2001, and April 11, 2001) has provided EECs (screening-level drinking water assessment) using simulation models to estimate the potential concentrations of thiophanate-methyl and MBC in ground and surface water.

4.3.2 Estimated Environmental Concentration (EECs)

EFED conducted screening-level assessments to generate EECs for thiophanate-methyl and MBC using the simulation models SCI-GROW (Tier 1) for ground water and Tier I GENEEC for ornamentals and turf use, and Tier 2 (PRZM/EXAMS) for onions for surface water. The modeling was conducted based on the environmental profile and the maximum seasonal application rate proposed for thiophanate-methyl uses based on the product label for ornamentals (76.6 lbs ai thiophanate-methyl/acre with 6 treatments per year at 14 day intervals), turf (15 lbs ai/acre with 6 treatments per season) and onions (15 lb ai/acre once per season). Thiophanate-methyl and MBC have the potential to pollute surface waters by erosion of soil particles to which these chemicals are adsorbed or via dissolution in runoff water, especially in areas with large amounts of annual rainfall that could result in large volumes of runoff.

The EECs are shown on Table 8. It is HED policy to divide the 56-day average tier I GENEEC EECs by a factor of 3 (HED SOP 99.5 M. Stasikowski 8/1/99) for comparison to chronic DWLOCs. Therefore, the long-term (56-day) surface water EECs for ornamental and turf uses were divided by a factor of 3, as shown on Table 8.

Table 8 EFED ESTIMATED ENVIRONMENTAL CONCENTRATION (EECs)					
Chemical	Ground Water SCI-GROW (Fg/L) (a) (acute and chronic)	Surface Water GENEEC (Fg/L)			
		Acute (Peak)		Long-Term	
		GENEEC	PRZM/ EXAMS	GENEEC (56-day avg) (b)	PRZM/ EXAMS (36 yr mean)
Thiophanate-methyl	0.17 (ornamental) 0.033 (turf) 0.006 (onions)	2,100 (ornamental) 420 (turf)	50 (onions)	1100/ 3=367 (ornamentals) 220/3=73.3 (turf)	0.44 (onions)
MBC	15 (ornamental) 3 (turf) 0.51 (onions)	1,600 (ornamental) 320 (turf)	210 (onions)	730/3=243 (ornamental) 150/3 = 50 (turf)	73.5 (onions)

(a) SCI-GROW (Screening Concentration in Ground Water) is an empirical model for predicting pesticide levels in ground water. The value from SCI-GROW is considered an upper bound concentration estimate.

(b) It is HED policy to divide the long-term tier I GENEEC EEC by a factor of 3 (HED SOP 99.5 M. Stasikowski 8/1/99).

EFED notes that MBC ground and surface water EECs are based on ornamental, turf, and onion uses, and are expected to provide the highest environmental exposures resulting from thiophanate-methyl use. As stated in the EFED memorandum (R. Pisigian, 1/19/01, and 4/04/01), the screening-level models used to estimate the maximum concentrations of thiophanate-methyl and MBC in surface water (GENEEC and PRZM/EXAMS) can substantially overestimate true drinking water concentrations. GENEEC assumes that the drinking water source is a 1 hectare pond with no mixing or dilution, that the entire watershed surrounding the pond is cropped and treated, and no treatment of the drinking water source. Therefore, these EECs are considered to be upper-bound, and it may be necessary to further refine these EECs.

4.4 Residential Exposure/Risk Pathway

This assessment for thiophanate-methyl reflects the Agency's current approaches for completing residential exposure assessments based on the guidance provided in the *Draft: Series 875-Occupational and Residential Exposure Test Guidelines, Group B-Postapplication Exposure Monitoring Test Guidelines*, the *Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment*, and the *Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment* presented at the September 1999 meeting of the FIFRA Scientific Advisory Panel (SAP). The Agency is, however, currently in the process of revising its guidance for completing these types of assessments. Modifications to this assessment shall be incorporated as updated guidance becomes available. This will include expanding the scope of the residential exposure assessments by developing guidance for characterizing exposures from other sources already not addressed such as from spray drift; residential residue track-in; exposures to farm worker children; and exposures to children in schools.

4.4.1. Residential Handler

Exposure Scenarios

Potential residential exposures can occur as a result of residential application of liquid, wettable powder and granular formulations to lawns. There are several granular home lawn products produced by the Scotts Company for residential application to lawns. All are a combination fertilizer/pesticide, or "weed and feed" formulations, ranging from 2 to 5% thiophanate-methyl by weight. It should be noted, that the current labels do not permit residents to treat home orchards, although a pest control operator (PCO) may treat home orchards. The following eight residential handler scenarios were evaluated:

(1) Applying with a ready-to-use hose-end sprayer;
(2) Mixing/loading/Applying liquid with a hose-end sprayer;
(3) Mixing/Loading/Applying wettable powder with a low pressure hand wand;
(4) Mixing/Loading/Applying liquids with a low pressure hand wand;
(5) Mixing/Loading/Applying with a backpack sprayer;
(6) Loading/Applying granular formulations with a push type spreader;
(7) Loading/Applying granular formulations with a belly grinder; and
(8) Hand dispersal of granules.

Some labels, such as a wettable formulation, may not be intended for consumer use, but do not restrict such usage on the current labels.

Exposure Data and Assumptions

The duration of exposure is expected to be short-term (1-7 days) for residential handlers during application of thiophanate-methyl products to turf and ornamentals. Intermediate- and long-term exposures of residential applicators are not anticipated based on thiophanate-methyl's use pattern and information from the registrant. Based on toxicological criteria and potential for exposure, HED has conducted a dermal and inhalation exposure assessments. Only exposures to thiophanate-methyl were evaluated, because MBC is formed during environmental degradation of thiophanate-methyl.

Residential usage patterns were estimated based on maximum label rate, label application frequency, estimated seasonal length, and persistence of thiophanate-methyl. Based on label information, thiophanate-methyl may be applied repeatedly to treat fungal infections. However, consultation with EPA agronomists (scientists) and information supplied by the registrant indicate that typical use is once per season over a lifetime. Therefore, it was estimated that thiophante methyl formulations could be applied once in season, and that residents treat 0.5 acres for broadcast application and 1,000 ft^2 for spot treatment. In addition, a 0.25 acre treated area was assumed for ornamental treatment with a ready-to-use hose end sprayer based on the label. The granular residential use label does not specify hand use for spot treatment, but only recommends application rates by spreader, and in one case states “do not apply by hand [Reg. No. 538-140]”. Nevertheless, a hand application was conservatively assessed. The registrant states that a belly grinder is not used to apply thiophanate-methyl granular formulations. However, this scenario was assessed because the labels do not specifically exclude application with a belly grinder, and this is the equipment type of choice for many homeowners. Both the belly grinder and hand-dispersed methods (like other hand-controlled applications) are low confidence estimates, but are considered to be generally conservative. If hand broadcast application and use of a belly grinder is to be prevented, the labels should be modified to specifically exclude these application methods. No chemical-specific data were submitted for residential handler risk assessment, so the PHED values were used, as cited in the Draft SOPs for Residential Exposure Assessments (12/97). For all residential equipment, the exposure estimates assume that individuals wear short pants, short sleeves and no gloves.

HED also estimated cancer risks based on the number of years typically working in the home garden (50 years) and lifetime (70 years), which are population defaults recommended by EPA's Exposure Factors Handbook. Therefore, cancer risks are based on 50 applications in a lifetime. A cancer risk assessment is considered appropriate because thiophanate-methyl has been assesses as a carcinogen using a model for carcinogenesis that assumes any exposure at any point in time may result in carcinogenic effects.

Risk Characterization

A summary of the short-term and cancer risk estimates for residential handler is presented in Table 9. As noted previously, non-cancer risk estimates are expressed in terms of the MOE. MOEs greater than 300 do not exceed HED's level of concern for residents. Cancer risks are presented as a probability of developing cancer over a lifetime.

Residential application of thiophanate-methyl formulated products to lawns and ornamentals at the maximum label rate resulted in risk estimates of concern (i.e., total MOE < 300) ranging from MOEs of 58-230 for all equipment types except (1) spot application with a ready to use hose-end sprayer (MOE=5,400 to5,800); (5) spot treatment with a backpack sprayer (MOE=3,500) and (6) loading/applying granules with a push type spreader to treat 0.5 acre (MOE=1,900). The MOEs of concern, are attributed primarily to dermal exposure. HED also evaluated lower application rates and spot treatments at the maximum label rate for the hose end sprayer, low pressure handwand and backpack sprayer to assist in risk management decisions. Most of these scenarios had total dermal and inhalation MOEs in the range of 770-37,000 and therefore, do not exceed HED's level of concern. The broadcast treatment estimates are based on treatment of 0.5 acre lawn per day, which is considered to be in the high-percentile range of lawn sizes. Recent lawn size survey data suggest that 0.5 acre represents 73% of the 2,300 respondents, while nearly 16% of the respondents had lawn sizes that ranged from 0.57 to 1 acre (Outdoor Residential use and Usage Survey and National Gardening Association Survey 1999). In this study, 2,300 respondents of 4,100 knew the size of their lawn. A spot treatment was assumed to be 1,000 ft^2. Note that hand dispersal is not an effective application method and may be eliminated by labeling restrictions. Both hand and spreader application exposures vary greatly with applicator technique.

Lifetime cancer risk estimates for applying thiophanate-methyl formulated products once per year for 50 years (i.e., 50 times in a lifetime) range from $5.2x10^{-9}$ to $4.5x\ 10^{-6}$ for a backpack sprayer and broadcast lawn treatment with a hose-end sprayer, respectively. Cancer risk estimates for the other application methods are in between these ranges. Only two scenarios have a cancer risk estimate that exceeds $1x10^{-6}$:

(2) Mixing/loading/applying liquids with a hose-end sprayer once per year for 50 years at the maximum rate for broadcast lawn treatment ($4.5x10^{-6}$), and

(8) hand dispersal of granules once per year for 50 years at the maximum rate for a spot treatment(3.2×10^{-6}).

Table 9 Short-Term Exposure and Risk Estimates (MOE) for Homeowner Lawn /Garden Application with Thiophanate-methyl										
Equipment Type	**Dermal Unit Exposure (mg/lb ai) (a)**	**Inhalation Unit Exposure (mg/lb ai) (b)**	**lb ai / acre (c)**	**Acres/ day (d)**	**Dermal Dose (non-absorbed) (mg/kg/day) (e)**	**Inhalation Dose (mg/kg/day) (f)**	**Dermal MOE (g)**	**Inhalation MOE (h)**	**Total MOE (i) (Target$300)**	**Cancer Risk Estimate (50 applications per lifetime)**
(1a) Applying with a RTU hose-end sprayer (ORETF data)	2.6	0.011	19.3 (turf)	0.025 (1,000 ft^2)	0.018	7.5E-5	5,600	130,000	5,400	7.2E-8
			1.8 (ornamentals)	0.25 (11,000 ft^2) (2 quarts product)	0.017	7.1E-5	6,000	140,000	5,800	3.4E-8
(1b) Mixing/loading/Applying liquid with a hose-end sprayer (ORETF data)	2.6	0.011	15	0.5	1.2	1.7E-3	**85**	5,800	**84**	**4.5E-6**
(2) Mixing/Loading/ Applying Wettable Powders with a Low Pressure Handwand	250	1.1	15	0.025 (1,000 ft^2)	1.34	5.9E-3	**75**	1,700	**72**	2.5E-7
			0.007 lb ai/gal	5 gal	0.13	5.5E-4	800	18,000	770	1E-6
(3) Mixing/Loading/ Applying Liquids with a Low Pressure Handwand	100	0.03	15	0.025 (1,000 ft^2)	0.54	1.6E-4	**190**	62,000	**190**	1E-6
			0.007 lb ai/gal	5 gal	0.05	1.5E-5	2,000	670,000	2,000	9.5E-8
(4) Mixing/Loading/ Applying with a Backpack Sprayer	5.1	0.03	15	0.025 (1,000 ft^2)	0.027	1.6E-4	3,700	62,000	3,500	5.6E-8
			0.007 lb ai/gal	5 gal	0.0026	1.5E-5	39,000	670,000	37,000	5.2E-9
(5) Loading/Applying with a Push-type Spreader (ORETF data)	0.68	0.00091	11	0.5	0.053	7.2E-5	1,900	140,000	1,900	Not applicable
			5.4		0.026	3.5E-5	3,800	280,000	3,700	5.1E-8
(6) Loading/Applying with a Belly Grinder	110	0.062	11	0.025 (1,000 ft^2)	0.43	2.4E-04	**230**	41,000	**230**	8.2E-7

Table 9 Short-Term Exposure and Risk Estimates (MOE) for Homeowner Lawn /Garden Application with Thiophanate-methyl										
Equipment Type	**Dermal Unit Exposure (mg/lb ai) (a)**	**Inhalation Unit Exposure (mg/lb ai) (b)**	**lb ai / acre (c)**	**Acres/ day (d)**	**Dermal Dose (non-absorbed) (mg/kg/day) (e)**	**Inhalation Dose (mg/kg/day) (f)**	**Dermal MOE (g)**	**Inhalation MOE (h)**	**Total MOE (i) (Target$300)**	**Cancer Risk Estimate (50 applications per lifetime)**
(7) Hand Dispersal of Granules	430	0.47	11	0.025 (1,000 ft^2)	1.67	1.8E-03	**59**	5,400	**58**	**3.2E-6**

* Values rounded to two significant figures
(a) Dermal unit exposure from PHED or ORETF where noted, represents short-sleeved shirt and shorts, no gloves; open mixing/loading and application by same person.
(b) Inhalation unit exposure from PHED or ORETF where noted; no respirator.
‘(c) Range of application rates based on labels.
(d) Amounts of acreage treated per day are from the Residential SOP for area treated in a single day for each exposure scenario of concern.
(e) Daily Dermal Dose (mg/kg/day) = [Dermal Exposure (UE mg/lb ai * lb ai/acre] / Body Weight (70 kg)]..
(f) Daily Inhalation Dose (mg/kg/day) = [Inhalation Exposure (UE mg/lb ai * lb ai/day = mg ai/day] / Body Weight (70 kg)].
(g) Dermal MOE = NOAEL (100 mg/kg/day) / Daily Dermal Dose mg/kg/day). Dermal NOAEL from a dermal study, therefore, no adjustment is made for dermal absorption.
(h) Inhalation MOE = NOAEL (10 mg/kg/day) / Daily Inhalation Dose (mg/kg/day).
(i) Total MOE = 1/ (1/MOE dermal + 1/MOE inhalation).

4.4.2 Postapplication Residential

Exposure Data and Assumptions

Potential residential postapplication exposures to adults and children may occur as a result of residential application or professional lawn care operator application of thiophanate-methyl products. Specifically, adult and child exposures were evaluated as a result of ornamental, fruit tree, golf course, and recreational and home lawn uses. Guidance from the Agency's Residential SOPs (Draft 1997, and February 22, 2001 update, ExpoSac policy 12) was used to address the exposures of children contacting recently treated turf, ornamentals or fruit trees. The SOPs use a high contact activity based on the use of Jazzercise® to represent the exposures of an actively playing child. All residential scenarios, where possible, utilized the thiophanate-methyl specific study data, which were modified by application rates from product labels. At a minimum, "typical," and high application rates were used in calculations.

The following residential postapplication scenarios were evaluated:

(1) Dermal exposure to adults, and adolescents involved in harvesting treated fruit in a home orchard;
(2) Dermal exposure to adults and young children involved in a high exposure activity, such as heavy yardwork or playing on treated turf;
(3) Dermal exposure to adults and adolescents (10-12 years) mowing or other moderate contact activity for 2 hours;
(4) Dermal exposure to adults and adolescents (10–12 years) involved in a low exposure activity, such as golfing or walking on treated turf;
(5) Incidental oral exposure to children (1-6 years) playing on treated turf
    (5a) turf mouthing,
    (5b) hand to mouth,
    (5c) granular ingestion, and
    (5d) incidental soil ingestion.

The Agency believes that thiophanate-methyl and MBC exposures can occur over a single day or up to weeks at a time even though established turf and ornamentals are generally treated 1-5 times per season. This is supported by the length of time that residues took to decline in the thiophanate-methyl strawberry and turf DFR studies submitted and the fact that several areas may be treated at different times. For example, a golf course or lawn might be treated over several weeks. The Agency classifies these as short-term exposures (one-week or less) and intermediate-term exposures (seven days to several months), respectively. No long-term (six months or more) residential exposures are associated with the use of thiophanate-methyl, due to the product's use pattern. These classifications are the basis for selecting toxicological endpoints for chemicals and are generally included in each risk assessment. Inhalation exposures are thought to be negligible in outdoor post-application scenarios relative to dermal and oral exposures because of the low vapor pressure of thiophanate-methyl (1.3×10^{-5} mmHg) and MBC (1×10^{-7} mmHg) and because the uses (and primary exposures) are outdoors allowing for significant dilution. As such, inhalation exposures are not considered in the post-application exposure assessment.

Dermal contact with treated turf residues (1-14 days following treatment) was evaluated for both adults and adolescents. The standard SOP recommended-assumptions were used, including 2 hours/day, 2 days/year for mowing, 14 days/year for dermal contact, short-term transfer coefficients of 14,500 and 5,200 cm^2/hour and intermediate-term transfer coefficients of 7,300 and 2,600 cm^2/hour for adults and children, respectively. Chemical-specific turf transfer residue data from the registrant were also used. Post-application exposures during fruit harvesting were based on adults and adolescents picking fruit 1-7 days following treatment, 20-40 minutes/day, for 5 days/year, and using transfer coefficients of 10,000 and 5,000 cm^2/hour for adults and adolescents, respectively. The residues were based on apple data submitted by the registrant. The golfing scenario assumed adults and adolescents could contact treated turf on the day of treatment (DAT 0 residues), 4 hours/day for 5 days/year. The SOP-recommended transfer coefficient of 500 cm^2/hour was used. The body weights used in the assessment are 15 kg, 39 kg, 60 kg and 70 kg for the child (1-6 years), adolescent 10-12 years, adult female, and adults (male and female), respectively. An adult female body weight of 60 kg was used to assess dermal MBC exposures, because the toxicological endpoint is based on a development effects. For the cancer assessment, it was assumed that individuals could contact thiophanate-methyl and MBC residues over a 50 year period based on the Residential SOPs.

Residential risk estimates utilized the submitted residue dissipation studies and a turf transfer study, as well as the EPA's original (12/97) and revised 2001 SOPs for Residential Exposure Assessment (ExpoSac Policy 12, February 22, 2001). Wherever available, reported usage data are used in this process to define values such as application rates and application frequency. The Agency always completes risk assessments using maximum application rates for each scenario because what is possible under the label (the legal means of controlling pesticide use) must be evaluated, for complete stewardship in order to ensure the Agency has no concern for the specific use. Additionally, whenever the Agency has additional information, such as minimum application rates or application frequency, it uses the information to further evaluate the overall risks associated with the use of the chemical (e.g., the study data based on 2 applications at typical rates were used for the thiophanate-methyl post-application risk assessment). All non-cancer risks (i.e., MOEs) for turf exposure were based on the maximum label application rate of 19.3 lb ai/acre for liquid formulations and 11 lb ai/acre for granular formulations, except for golf course exposures, which were assessed at a maximum rate of 15 lb ai/acre. However, for cancer risk estimates, a typical turf application rate of 5.4 lb ai/acre was used, based on information from the registrant. For fruit harvesting, the maximum application rate for peaches of 1.6 lb ai/acre was used to assess non-cancer risks, while a typical rate of 1.3 lb ai/acre was used to assess the cancer risks.

Risk Characterization

A summary of the short- and intermediate-term risk estimates for residential/non-occupational postapplication dermal and incidental oral exposures is presented in Table 10. As noted previously, non-cancer risk estimates are expressed in terms of the MOE. MOEs $ 300 for exposures to thiophanate-methyl and MOEs $1000 for exposures to MBC do not exceed HED's level of concern for residents, children or other non-occupationally exposed individuals (i.e., golfers). Cancer risk estimates are expressed as a probability of developing cancer over a lifetime. Postapplication exposures were evaluated for both thiophanate-methyl and MBC.

Thiophanate-methyl

All short-term MOEs for children playing on treated turf were less than 300 and therefore, exceed

HED's level of concern (MOEs range from 9 to 240), except incidental soil ingestion (MOE=10,000). The aggregate MOE for children based on combined dermal and oral exposures is also well below 300 (total MOE=21-46 for treated turf). In addition, short-term MOEs were less than 300 for adults during high dermal contact (such as hand weeding, etc) where MOEs range from 140 to 240 for treated turf. However, all short-term MOEs for adolescents and adults involved in mowing and golf activities are greater than 300, and therefore, do not exceed HED's level of concern. These MOEs were based on turf transfer residue (TTR) data provided by Elf-Atochem for the day of treatment, and transfer rates recommended in the EPA Residential SOPs. As noted previously, the short-term MOEs are based on contact with residues on the day of treatment. HED also assessed intermediate-term dermal exposure for children playing on treated lawns using the lower residues present seven days after treatment. As shown on Table 10, all intermediate-term dermal MOEs are greater than 300 and therefore, do not exceed HED's level of concern.

The short-term MOEs for adults harvesting fruit one day after it was sprayed at the typical rate for Topsin M (70% WP) (1.6 lb ai/acre for peaches for non-cancer and 1.3 lb ai/acre for cancer) were also less than 300 (MOE=210), and therefore exceed HED's level of concern. However, the MOEs are greater than 300 for adolescents harvesting fruit on the day of treatment (MOE=470), and for adults harvesting fruit seven days following thiophanate-methyl application (MOE=780). These MOEs were based on registrant-submitted data for apple trees, and assumed adults and adolescents harvested apples for 40 and 20 minutes per day, respectively, 5 days/year.

HED also estimated cancer risks using the same residential exposure scenarios. The lifetime cancer risks ranged from 1.9×10^{-8} to 3.7×10^{-6} for the scenarios evaluated (mowing and harvesting fruit, respectively). The highest cancer risks are based on harvesting home orchards 40 minutes/day, 5 days per year for 50 years, which yields an elevated cancer risk estimate of 3.7×10^{-6} for contact with residues on the day after treatment (DAT 1), and 1×10^{-6} for contact with the 7-day average residues (7 DAT). The Agency endeavors to reduce estimated cancer risks for the general population to less than one in one million (10^{-6}).

MBC

Potential post-application exposures and risks to MBC residues were also evaluated using the same protocols and the highest MBC residue levels from each corresponding study. All MOEs were above 1000 and therefore do not exceed HED's level of concern, except the child hand to mouth scenario (MOE=910). The risk estimates for dermal contact with turf ranged from a low MOE of 5,800 for a child playing on a lawn to a high MOE of 420,000 for an adult female mowing a lawn for 2 hours. The MOE estimates for toddler oral exposure via turf mouthing (MOE=15,000) were above 1000. It should be noted that MBC exposure estimates are not based on day-of-application levels, because MBC residues increase for a period of time while thiophanate-methyl residues decline, then both compounds decline. For each scenario, the maximum detected MBC residue was used (which in some cases was at day 14). The registrant-data show that low level residues of MBC are present up to 2 weeks following thiophanate-methyl lawn treatment.

Adult lifetime cancer risks were also estimated for MBC post-application residential exposure, using foliar residues from apple and turf studies, and all scenarios had risks below 10^{-6}. The highest cancer risk estimate for MBC alone was 8.6×10^{-8} for adults harvesting fruit 5 days/year.

The Residential SOPs are considered to be conservative scenarios for determining risk estimates. The adult and toddler transfer coefficients are based on the Jazzercise protocol and an upper percentile exposure duration value. Where study data were used with the SOP formulae, these risk estimates were better refined, and hence, less conservative. Therefore, the dermal exposure estimates related to lawn and orchard skin contact (which were based on study data) are more refined than the estimates of incidental ingestion of thiophanate-methyl or MBC residues.

The median frequency of postapplication exposure to golf course turf is based on data provided by golfing associations. Therefore the risk estimates associated with golfing are believed to be average, or not over-estimated. The residential exposure to treated lawns or tree foliage is based upon exposure to transferable residues at the earliest possible opportunity and high transfer coefficients. While this is a high-end scenario, it is not worst-case because the time of exposure is short, based on behavioral data, and the risk estimate is based on actual data supplied by the registrant, which did not use the highest rate or number of applications for turf.

Mitigating circumstances for homeowner/residential exposure to thiophanate-methyl residues may include the watering-in of both liquid and granular formulations on turf. There is some evidence from the study data submitted that watering or rainfall increases the residue dissipation rate [see summaries of Turf TTR study; also Apple study, NY (wet) vs. WA (dry) data]. Turf labels variously call for watering or irrigation within 24 hours or less. This instruction, however, does not prevent contact with turf prior to watering-in.

Table 10 Potential Post-Application Exposures and Risks for Residential/Non-Occupational Uses of Thiophanate-methyl (Short- and Intermediate-term)										
Duration of Exposure (c)	**Application Rate lb ai/A**	**Maximum Potential Dose (a) (mg/kg/day) / MOE (unitless) Target MOE$300 for TM and $1000 for MBC**						**Cancer Risk Estimate (c,d)**		
		Child 1-6 years (15 kg)		**Adolescent 10-12 years (39 kg)**		**Adult (Includes females ≥ 13 years)**				
		TM	**MBC exposure (absorbed dose)**	**TM**	**MBC exposure (absorbed dose)**	**TM**	**MBC exposure (absorbed dose)**	**TM**	**MBC**	**Total TM and MBC**
(1) Dermal Exposure During Treated Fruit Harvesting										
Short-Term	1.6 NC/1.3 C (based on peaches)	NA	NA	0.21 MOE= 470	0.026 (0.00091) MOE=11,000	**0.48 MOE= 210**	0.069 (0.0024) MOE=4,100	**3.7E-6**	4.6E-8	**3.7E-6**
Intermediate-term				0.056 MOE= 1,800		0.128 MOE= 780		1E-6	8.6E-8	**1.2E-6**
(2) Dermal Contact with Treated Turf										
Short-term	19.3 NC/5.4C	**1.2 MOE = 81**	0.049 (0.0017) MOE =5,800	Not calculated		**0.74 MOE = 140**	0.034 (0.0012) MOE=8,300	9.6E-7	6.7E-9	9.7E-7
	11 NC/5.4 C	**0.7 MOE=140**	0.028 (0.00098) MOE=10,000			**0.42 MOE= 240**	0.0197 (0.00069) MOE=15,000			
Intermediate-term	19.3 NC/5.4C	0.19 MOE=540	0.025 (0.00086) MOE=12,000			0.11 MOE = 890	0.017 (0.006) MOE=17,000			
	11 NC/5.4 C	0.106 MOE=940	0.0014 (0.000049) MOE=20,000			0.064 MOE= 1,600	0.01 (0.0035) MOE= 29,000			
(3) Dermal Contact During Mowing Treated Turf										
Short- and intermediate-term	19.3 NC/5.4C	NA		0.046 MOE = 2,200	0.0018 (0.000064) MOE = 160,000	0.025 MOE = 3,900	0.0012 (0.000042) MOE = 240,000	1.9E-8	1.3E-10	1.9E-8
	11 NC/5.4 C			0.026 MOE= 3,800	0.001 (0.000036) MOE= 270,000	0.014 MOE= 6,900	0.000686 (0.000024) MOE= 420,000			

Table 10 Potential Post-Application Exposures and Risks for Residential/Non-Occupational Uses of Thiophanate-methyl (Short- and Intermediate-term)										
Duration of Exposure (c)	**Application Rate lb ai/A**	**Maximum Potential Dose (a) (mg/kg/day) / MOE (unitless) Target MOE$300 for TM and $1000 for MBC**						**Cancer Risk Estimate (c,d)**		
		Child 1-6 years (15 kg)		**Adolescent 10-12 years (39 kg)**		**Adult (Includes females > 13 years)**				
		TM	**MBC exposure (absorbed dose)**	**TM**	**MBC exposure (absorbed dose)**	**TM**	**MBC exposure (absorbed dose)**	**TM**	**MBC**	**Total TM and MBC**
(4) Dermal Contact During Golfing or walking										
Short- and intermediate-term	15 NC/5.4 C	NA		0.071 MOE =1,400	0.0028 (0.000098) MOE = 100,000	0.039 MOE =2,500	0.0018 (0.000063) MOE = 160,000	4.7E-8	3.3E-10	4.7E-8
	11 NC/5.4 C			0.052 MOE= 1,900	0.0021 (0.000074) MOE= 140,000	0.029 MOE= 3,500	0.0013 (0.000046) MOE= 210,000			
(5a) Turf Mouthing										
Short- and intermediate-term	19.3	**0.072 MOE=140**	0.00064 MOE= 15,000	NE		NE		NE		
	11	**0.041 MOE=240**								
(5b) Hand to Mouth										
Short-and intermediate-term	19.3	**0.29 MOE = 35**	**0.011 MOE = 910**	NE		NE		NE		
	11	**0.16 MOE=61**								
(5c) Granular Ingestion										
Short-and intermediate-term	11	**0.32 - 1.1 MOE = 9-31**	not calculated	NE		NE		NE		
(5d) Incidental Soil Ingestion										
Short-and intermediate-term	19.3	0.00097 MOE= 10,000	not calculated	NE		NE		NE		
	11	0.00055 MOE= 18,000								
Aggregate MOE (b)	19.3 Short-term	**21**	NA (different endpoints)							
	19.3 Intermediate-term	**27**								
	11 Short-term	**37**								

Table 10
Potential Post-Application Exposures and Risks for Residential/Non-Occupational Uses of Thiophanate-methyl
(Short- and Intermediate-term)

Duration of Exposure (c)	Application Rate lb ai/A	Maximum Potential Dose (a) (mg/kg/day) / MOE (unitless) Target MOE$300 for TM and $1000 for MBC						Cancer Risk Estimate (c,d)		
		Child 1-6 years (15 kg)		Adolescent 10-12 years (39 kg)		Adult (Includes females > 13 years)				
		TM	MBC exposure (absorbed dose)	TM	MBC exposure (absorbed dose)	TM	MBC exposure (absorbed dose)	TM	MBC	Total TM and MBC
	11 Intermediate-term	46								

NA = Not applicable; NC=non cancer; C=cancer
NE = Not evaluated, because scenario not applicable to this population.
(a) Potential Dose not adjusted for absorption.
(b) Aggregate MOE for children 1-6 years includes dermal, turf mouthing, hand to mouth and incidental soil ingestion. There is a common endpoint of decreased body weight and food consumption for oral and dermal exposures.
(c) For thiophanate-methyl cancer risks for fruit harvesting, residues based on day after treatment (DAT 1) for short-term, DAT 7 for intermediate-term for fruit harvesting. MBC cancer risks for fruit harvesting based on maximum detected residues (on day 14 post treatment). For turf, cancer risks for thiophanate-methyl based on 14 day average residues, while cancer risks for MBC are based on the maximum residue.
(d) Cancer risks based on contact 5 days/year, 14 days/year, 2 days/year and 5 days/year for 50 years for fruit harvesting, dermal lawn contact, mowing and golfing, respectively.
MOE_{dermal} = NOAEL / (Max Potential Dose * dermal/oral route conversion) . MBC oral NOAEL = 10 mg/kg/day, 3.5% dermal absorption. TM: dermal NOAEL = 100 mg/kg/day (no absorption necessary).
MOE_{oral} = oral NOAEL / (Max Potential Dose). MBC oral NOAEL = 10 mg/kg/day. TM oral NOAEL = 10 mg/kg/day
LADD = [Absorbed Dermal Dose * Exposure Days/Yr * 50 years] / [70 years lifetime * 365 days/year] * 60/70 oral/dermal endpoint body weight correction (for MBC only)
Cancer Risk = LADD * cancer Q_1, where Q1* = 0.00239 $(mg/kg/day)^{-1}$ for MBC and $1.38x10^{-2}$ (mg/kg/day)-1 for thiophanate-methyl.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

For establishing a pesticide tolerance, the Food Quality Protection Act amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA, Section 408(b)(2)(A)(ii)) require "that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there are reliable information." Aggregate exposure is the total exposure to a single chemical (or its residues) that may occur from dietary (i.e., food and drinking water), residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation). Aggregate risk assessments were conducted for acute (1 day), short-term (1-7 days), intermediate-term (7 days to several months), and chronic (several months to lifetime) exposures to thiophanate-methyl and MBC. The aggregate risk assessments for chronic exposures includes a non-cancer and a cancer assessment. In all, five aggregate risk assessments were conducted.

As part of the aggregate assessment, HED conducted the aggregate assessments under two scenarios: (1) one that considered thiophanate-methyl and MBC exposures resulting exclusively from thiophanate-methyl uses and, (2) thiophanate-methyl and MBC from all uses, including thiophanate-methyl and registered MBC uses. These aggregate assessments are referred to as Aggregate 1 and Aggregate 2, respectively.

Aggregate 1 Assessment. Because thiophanate-methyl and MBC have common acute and chronic toxicity endpoints [developmental effects for females (13-50 years), and liver effects and tumors for chronic exposures for all subpopulations], and individuals are likely to consume both residues simultaneously on a given food commodity, it is appropriate to add thiophanate-methyl and MBC dietary risk estimates for females (13-50 years) under the acute dietary assessment, and for all subpopulations under the chronic dietary assessment. In addition, there are short- and intermediate-term residential and other non-occupational exposures (e.g., golf course use) to thiophanate-methyl, or to MBC resulting from thiophanate-methyl uses. Therefore, residential/non-occupational dermal exposures are also anticipated to occur for the Aggregate 1 assessment. Consequently, aggregate exposures and risks from exposure to these compounds in food and water sources, and as a result of residential/non-occupational uses will be characterized for thiophanate-methyl and MBC (resulting from thiophanate-methyl uses) under the Aggregate 1 assessment.

Aggregate 2 Assessment. Dietary exposures to MBC may occur from benomyl or thiophanate-methyl application to food crops because MBC is the primary environmental and metabolic degradate of both fungicides. However, in April 2001, the benomyl registrant requested voluntary cancellation of all benomyl-containing products, with sales and distribution proposed to cease by December 31, 2001 (http://www.dupont.com, April 19, 2001). Consequently, MBC exposures from benomyl uses were not evaluated in this assessment. MBC exposures (dermal and oral) can also occur from registered residential and recreational thiophanate-methyl uses including lawn treatment, golf courses and home orchards. In addition, MBC is registered for tree injection and as a fungicide/preservative in paints, coatings, plaster, and adhesives in residential settings. Consequently, residents could be exposed to registered MBC products via dermal and inhalation exposure during painting activities, and via inhalation of vapors in painted rooms. Residential exposures resulting from tree injection uses are considered to be negligible.

Therefore, the Aggregate 2 assessment includes MBC exposures from all dietary (food and water from thiophanate-methyl uses) and residential/recreational uses (from thiophanate-methyl and MBC use). In addition, thiophanate-methyl risk estimates were combined with the total MBC risk estimates only for females and for chronic exposures because of common toxicity endpoints and simultaneous exposure on thiophanate-methyl-treated commodities.

5.1 Acute Aggregate Risk

The acute aggregate risk estimate to thiophanate-methyl and MBC addresses exposure from food and water. For the Tier III acute dietary exposure analysis, field trial data level residues in conjunction with percent crop treated data were used to assess dietary exposures.

5.1.1 Aggregate 1: Thiophanate-methyl and MBC (from Thiophanate-methyl Use)

5.1.1.1 Aggregate Acute Risk Assessment

The thiophanate-methyl acute dietary risk estimates range from 8.6% to 21.4% of the aPAD for thiophanate-methyl, with infants (<1 years old) being the highest exposed population subgroup. For MBC, the acute dietary risk estimates range from 4% to 108%, with highest risk estimates for infants (< 1 yrs old). Thus, the acute dietary (food) risk estimate associated with MBC exposure alone exceeds the Agency's level of concern. [The acute aggregate risk assessment conducted under scenario 1 is the same as that conducted for the acute dietary risk assessment.]

Because thiophanate-methyl and MBC have a common acute toxicity endpoint for females (13-50 years) based on developmental effects, it is appropriate to add thiophanate-methyl and MBC acute dietary risk estimates for this subpopulation. In addition, individuals are likely to consume both residues simultaneously on a given food commodity. The total thiophanate-methyl and MBC acute dietary risk estimate is 57.6% of the aPAD for developmental effects for females of child bearing age (13-50 years). Acute dietary risk estimates were not combined for thiophanate-methyl and MBC for other populations because the acute oral endpoint for these other populations is based on different effects (i.e., tremors for thiophanate-methyl and testicular effects for MBC).

The acute aggregate assessment includes both dietary and drinking water exposures to thiophanate-methyl and MBC. Drinking water monitoring data are not available, therefore, HED calculated drinking water level of comparisons (DWLOCs), which are discussed below to account for potential drinking water exposures to thiophanate-methyl and MBC.

5.1.1.2 Acute DWLOC Calculations

A drinking water level of comparison (DWLOC) is the concentration of a pesticide in drinking water that would result in risk estimates below HED's level of concern, when considering total aggregate exposure to that pesticide from food, water, and residential uses. HED uses DWLOCs in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for a pesticide, the DWLOC is used as a point of comparison against the conservative EECs provided by computer modeling (SCI-GROW, GENEEC, PRZM/EXAMS).

HED back-calculates the acute DWLOCs by a two-step process: exposure [food + (if applicable) residential exposure] is subtracted from the acute PAD to obtain the maximum exposure allowed in drinking water; DWLOCs are then calculated using that value and HED default body weight and drinking water consumption figures. A DWLOC may vary with drinking water consumption patterns and body weights for specific subpopulations. In assessing human health risk, the acute DWLOCs are compared to acute (maximum) EECs. When EECs are **greater** than DWLOCs, HED considers the aggregate risk estimates [from food + water + (if applicable) residential exposures] to exceed HED's level of concern (HED SOP 99.5 "Standard Operating Procedures for Incorporating Estimates of Drinking Water Exposure into Aggregate Risk Assessment, August 1, 1999).

DWLOCs based on simultaneous dietary exposure to both thiophanate-methyl and MBC (as MBC equivalents) were estimated using the aPAD for MBC and by combining the 99.9th percentile dietary exposure for both chemicals. As noted previously, a TEF approach was used to convert the thiophanate-methyl dietary exposure into MBC equivalents. Table 11 presents the total dietary exposure estimate as MBC equivalents.

The acute DWLOC values are also presented in Table 11. For each population subgroup listed, the acute PAD and the acute dietary (food) exposure (from Table 6) as MBC equivalents, for that subgroup were used to calculate the acute DWLOC for the subgroup, using the formulas in footnotes of Table 11.

Using conservative screening-level models, the acute (maximum) estimated environmental concentrations (EECs) of thiophanate-methyl in groundwater (SCI-GROW) range from 0.006 to 0.17 Fg/L, while the surface water EECs range from 50 to 2,100 Fg/L. Because thiophante-methyl rapidly degrades to MBC within hours to days, EFED also provided EECs for MBC in groundwater (SCI-GROW) that range from 0.51 to 15 Fg/L, and surface water EECs that range from 210 to 1,600 Fg/L. As noted previously, a TEF approach was used to convert the thiophanate-methyl dietary exposure into MBC equivalents (i.e., factor of 0.15 was applied to the thiophanate-methyl dietary exposure estimates for females) in order to aggregate thiophanate-methyl and MBC dietary and drinking water exposures and risks.

As shown on Table 11, the acute DWLOC is effectively zero for infants (<1 year old) because the acute dietary exposure to MBC alone exceeds HED's level of concern (i.e., >100% aPAD). Therefore, potential drinking water exposures will only further contribute to exposures of concern. For children (1-6 years) and females of child bearing age (13-50 years) the acute MBC EECs for surface water (but not groundwater) of 210 to 1,600 Fg/L exceed the acute DWLOCs (31 and 130 Fg/L, respectively), indicating that food and drinking water could exceed HED's level of concern for these subpopulations. As noted previously, when EECs are **greater** than DWLOCs, HED considers the aggregate risk [from food + water] to exceed HED's level of concern. It should be noted that neither SCI-GROW, GENEEC nor PRZM/EXAMS models reflect concentrations after dilution (from source to treatment to tap) or treatment of drinking water. As stated in the EFED memorandum (R. Pisigian, 1/19/01,a dn 04/04/01), the screening-level model used to estimate the maximum concentrations of thiophanate-methyl and MBC in surface water can substantially overestimate actual drinking water concentrations. GENEEC assumes that the drinking water source is a 1 hectare pond with no mixing or dilution, that the entire watershed surrounding the pond is cropped and treated, and no treatment of the drinking water source. Therefore, these EECs are considered to be upper-bound, and it will be necessary to refine the GENEEC estimates for turf and ornamentals.

HED concludes that **acute aggregate exposure thiophanate-methyl and MBC in food and water exceeds the HED's level of concern for infants, children (1-6 years) and females (13-50 years).**

<table>
<tr><th colspan="7">Table 11
DWLOCs FOR ACUTE AGGREGATE 1 DIETARY EXPOSURE
Thiophanate-methyl AND MBC (From TM Use)</th></tr>
<tr><th>Population Subgroup (a)</th><th>MBC Acute PAD (mg/kg/day)</th><th>Total Food Exposure as MBC Equivalents (mg/kg/day) (b)</th><th>Max. Water Exposure (mg/kg/day) c)</th><th>Surface Water (Fg/L)</th><th>Ground Water SCI-GROW (Fg/L)</th><th>MBC Acute DWLOC (Fg/L) (d,e,f)</th></tr>
<tr><td>U.S. Population</td><td>0.17</td><td>0.006838
(MBC only)</td><td>0.163</td><td rowspan="4">210 to 1,600
(MBC)

50 to 2,100 (TM)</td><td rowspan="4">0.51 to 15
(MBC)

0.006 to 0.17
(TM)</td><td>5,700</td></tr>
<tr><td>All Infants (< 1 Year)</td><td>0.017</td><td>0.018429
(MBC only)</td><td>zero (no room)</td><td>zero
(no room)</td></tr>
<tr><td>Children (1-6 years)</td><td>0.017</td><td>0.01391
(MBC only)</td><td>0.0031</td><td>31</td></tr>
<tr><td>Females
(13-50 years)</td><td>0.01</td><td>0.00576</td><td>0.00424</td><td>130</td></tr>
</table>

(a) In addition to the U.S. population (all seasons), the most highly exposed subgroup within each of the infants, children, female groups is listed.
(b) 99.9th percentile exposure. Values are from Table 6. Values for females based on TM and MBC exposure due to a common endpoint (developmental effects). Thiophanate-methyl exposure adjusted using the appropriate TEF of 0.15 for females. Values for other populations based on MBC alone due to different endpoints (testicular effects for MBC and tremors for TM).
C) Maximum Water Exposure (mg/kg/day) = Acute PAD (mg/kg/day) - Acute Food exposure (mg/kg/day).
(d) DWLOC (Fg/L) = Maximum water exposure (mg/kg/day) x body wt (kg) ÷ [(10^{-3} mg/Fg) x water consumed daily (L/day)].
(e) HED default body weights are: general U.S. population, 70 kg; adult females, 60 kg; and infants/children, 10 kg.
(f) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.

5.1.2 Aggregate 2: Thiophanate-methyl and MBC from all Uses

As noted previously, in April 2001, the benomyl registrant requested voluntary cancellation of all benomyl-containing products, with sales and distribution proposed to cease by December 31, 2001 (http://www.dupont.com, April 19, 2001). Consequently, MBC dietary exposures from benomyl uses were not evaluated in this assessment. MBC has no registered food uses in the U.S. Therefore, HED did not conduct an aggregate assessment of all MBC acute dietary exposure resulting from registered uses of both thiophanate-methyl and benomyl.

5.2 Short-Term Aggregate Risk

5.2.1 Aggregate 1: Thiophanate-methyl and MBC (from Thiophanate-methyl Uses)

Short-term aggregate risk estimates were not conducted for thiophanate-methyl and MBC because most of the short-term non-occupational exposures for both residential handlers (at the maximum label rate) and during post application activities result in MOEs less than 300 for thiophanate-methyl, and therefore already exceed HED's level of concern based on a screening-level assessment using the residential SOPs. Any additional short-term exposures through food and drinking water would result in MOEs that would further exceed HED's level of concern. Therefore, DWLOCs for short-term exposures to thiophanate-methyl and MBC in drinking water were not calculated, because the DWLOCs are effectively zero.

As shown on Tables 9 and 10, short- term handler MOEs for thiophanate-methyl range from 58 to 37,000 (spot treatment) for application of thiophanate-methyl products to lawns, while short-term dermal post application MOEs for thiophanate-methyl alone range from 210-470 for harvesting fruit, and 81-140 for dermal contact with treated turf by young children. MOEs for incidental ingestion of thiophanate-methyl residues on treated turf were also of concern and ranged from 9 to 240, except incidental soil ingestion. The thiophanate-methyl dermal and oral aggregate MOEs for a child (1-6 years) playing on a treated lawn ranges from 21 to 37. The postapplication MOEs for mowing treated turf and golfing are above 300 and do not exceed HED's level of concern. The MOEs for MBC resulting from post application exposures are all above 1000, except for hand to mouth activity by children (MOE=910) and therefore, do not exceed HED's level of concern, but do contribute to further overall exposures of concern.

5.2.2 Aggregate 2: Thiophanate-methyl and MBC from All Uses

5.2.2.1 Aggregate Short-Term Risk Assessment

For this assessment, HED evaluated the aggregate exposures to MBC resulting from registered uses of thiophanate-methyl and MBC. As noted previously, MBC is a major metabolite of thiophanate-methyl. The short-term aggregate risk estimate includes average dietary exposure (food and water) to MBC from thiophanate-methyl uses, and short-term non-occupational exposures to MBC (from thiophanate-methyl and MBC uses). Because thiophanate-methyl has residential and non-occupational uses (i.e., lawns, golf courses and residential orchards), the potential exposure to MBC from these uses was estimated and added to the average chronic dietary exposure. Estimated exposure from the residential uses of MBC as a paint additive were also added to the average chronic dietary MBC exposure. Thiophanate-methyl exposures were also considered due to similar toxic endpoints and concurrent exposure to thiophanate-methyl and MBC on commodities and lawns treated with thiophanate-methyl.

As noted in the Aggregate 1 assessment, most of the short-term non-occupational exposures for both residential handlers (at the maximum label rate) and during post application activities result in MOEs less than 300 for thiophanate-methyl, and therefore already exceed HED's level of concern based on a screening-level assessment using the residential SOPs. Therefore, any additional short-term exposures through food and drinking water would result in MOEs that would further exceed HED's level of concern. Nevertheless, HED conducted an aggregate assessment of thiophanate-methyl and MBC from all uses for informational purposes.

Table 12 presents the aggregate exposure estimates for MBC from diet and residential/non-occupational uses. Based on thiophanate-methyl uses, it was assumed that children (1-6 years) could be exposed to MBC and thiophanate-methyl residues through dermal contact with treated residential turf, and through turf mouthing, and incidental ingestion of residues on turf (i.e., hand to mouth activities). Incidental soil ingestion by children (1-6 years) was also evaluated for thiophanate-methyl, but not MBC. Children 7-12 years could contact MBC and thiophanate-methyl residues and be dermally exposed during mowing activities, harvesting fruit from a residential orchard, and playing golf. However, for this assessment, only the highest exposure scenario, harvesting fruit was aggregated with dietary exposures, because the dermal exposures from mowing and golfing were approximately an order of magnitude lower than the fruit harvesting exposures. Female residents were assumed to have MBC and thiophanate-methyl dermal exposures through harvesting treated fruit and contact with treated residential turf. Potential dermal exposures from mowing and golf activities were approximately an order of magnitude lower, and therefore, would have a negligible contribution to female exposure. Residents that apply thiophanate-methyl products to lawn and ornamentals are only expected to be exposed to thiophanate-methyl, and not MBC, because MBC is formed in the environment after application. Therefore, dermal exposures during a broadcast application of thiophanate-methyl liquid formulation were also included in the thiophanate-methyl aggregate exposure assessment for females 13-50 years. The results of this exposure analysis are presented in detail in the Occupational /Residential Exposure Chapter for the Reregistration Eligibility Document for Thiophante-Methyl (D271922, March 15, 2001).

In addition, based on MBC registered uses, it was assumed that adult residents could be exposed to MBC during painting activities (e.g., dermal and inhalation exposure during painting) and through the diet (food and water). The dermal and inhalation exposures associated with airless sprayers were used in the aggregate assessment. Details of the residential exposure assessment for registered MBC uses are presented in the attached memorandum from G. Bangs to D. Smegal, March, 2001, D273465. For this painting scenario, an adult resident was assumed to apply 2 gallons of paint containing 0.5% ai MBC, and wear short pants, short-sleeved shirt and no gloves. Exposure estimates were based on data from PHED. However, due to the very low vapor pressure of MBC relative to other pesticides, the risk estimates for MBC inhalation exposure are considered to be conservative. It was not considered reasonable to aggregate these MBC exposures with the lawn and orchard MBC exposures resulting from thiophanate-methyl use. Post application exposure to paint vapors containing MBC is considered a long-term exposure and consequently is considered in the cancer aggregate assessments (below). Long-term inhalation exposures were not aggregated with non-cancer risks because the endpoint of concern (respiratory effects) is different than the chronic oral endpoint (liver effects).

As noted previously, most of the short-term non-occupational exposures to thiophanate-methyl for both residential handlers and during post application activities result in MOEs less than 300, and therefore already exceed HED’s level of concern. As shown on Tables 9 and 10, short-term handler MOEs for thiophanate-methyl range from 58 to 37,000 (spot treatment) for application of thiophanate-methyl products to lawns, while dermal post application MOEs for thiophanate-methyl alone range from 210-470 for harvesting fruit, and 81-140 for dermal contact with treated turf. MOEs for incidental ingestion of thiophanate-methyl residues on treated turf were also of concern and ranged from 9 to 240, except incidental soil ingestion. The thiophanate-methyl dermal and oral aggregate MOEs for a child (1-6 years) playing on a treated lawn ranges from 21 to 37 for liquid and granular products, respectively. The postapplication MOEs for mowing treated turf and golfing are above 300 and do not exceed HED’s level of concern. The MOEs for MBC resulting from post application exposures are all above 1000, and therefore, do not exceed HED’s level of concern, but do contribute to further overall exposures of concern.

All oral exposures were compared to the short-term oral endpoint for MBC in accordance with HED policy. Only exposure and risk estimates associated with common toxicological endpoints were aggregated. For example, all oral MBC exposures and MOEs were aggregated. Thiophanate-methyl and MBC dermal exposures were evaluated separately and were not aggregated because the dermal endpoints are based on a different effects (i.e., decreased body weight and food consumption for thiophanate-methyl and developmental effects for MBC). Consequently, a toxic equivalency factor was not developed to adjust the thiophanate-methyl dermal exposures and risks into MBC equivalents. Therefore, the total aggregate risk estimates do not include the thiophanate-methyl dermal exposures (which are presented separately in Table 12). For females, both oral and dermal MBC risk estimates were aggregated because both endpoints are based on a NOAEL of 10 mg/kg/day for developmental effects and decreased body weight and food consumption. The MBC and thiophanate-methyl dermal exposure estimates were adjusted for 3.5% and 7% dermal absorption, respectively in calculating the dermal risk estimates. It is not appropriate to aggregate the inhalation MOEs with the oral and dermal MOEs because the inhalation NOAEL is based on respiratory effects.

As shown on Table12, aggregate MOEs are of concern for children 1-6 years and females (i.e., < 300 for thiophanate-methyl and <1000 for MBC). Consequently, any additional exposure from drinking water would only result in further exposures of concern. The short-term aggregate risk estimates for children 7-12 years (excluding drinking water) do not exceed HED’s level of concern.

5.2.2.2 Short-Term DWLOC Calculations

Aggregate potential MBC exposures, along with the EFED estimated EECs are presented on Table 13. The long term EFED MBC EECs range from 50 to 243 Fg/L from thiophanate-methyl use. As shown, the combined potential short-term exposure to MBC from food and residential use alone exceed HED’s level of concern for children 1-6 years and females 13-50 years, and therefore any water exposure would only contribute to the exposures of concern. For these subpopulations, the short-term DWLOCs are effectively zero. For children 7-12 years, the long-term MBC EEC in surface water is greater than the DWLOC, and therefore exceeds HED's level of concern based on thiophanate-methyl ornamental use. However, the EECs for turf and onion use of 50 and 73.5 Fg/L, respectively, for surface water and 3 and 0.51 Fg/L, respectively, for groundwater are less than the DWLOC of 95 Fg/L and therefore, do not exceed HED’s level of concern. In conclusion, **aggregate potential short-term exposure to MBC and thiophanate-methyl resulting from food, water and**

residential use due to thiophanate-methyl, and MBC uses exceeds HED's level of concern for children (infants, and 1-6 years of age) and females 13-50 years, due primarily to thiophanate-methyl post-application exposures on turf and ornamentals and MBC's use as a paint additive. This analysis is considered reasonable because HED aggregated some (but not all) of the possible residential/recreational use scenarios associated with thiophanate-methyl uses (i.e., excluded potential exposures to golfers, individuals mowing treated lawns) with dietary exposures to ensure this analysis is as realistic as possible.

Table 12
Summary of Aggregate Short-Term Exposure
Chronic Diet and Short-Term Residential Use
Aggregate 2: Thiophanate-methyl and MBC (From All Uses)
(Excludes Water)

Population Subgroup	Thiophanate-methyl Target MOE$300			MBC +other metabolites (from Thiophanate-methyl) Target MOE$1000			MBC (from MBC Uses) Target MOE$1000		Total Aggregate MOE Estimate (c) MBC Equivalents, unless noted Target MOE$1000 for MBC $ 300 for TM		
	Chronic Diet Exposure as TM and MBC equivalents (mg/kg BW/day) (a)/ MOE	Short-Term Residential Exposure (mg/kg/day)/ MOE		Chronic Diet Exposure (mg/kg BW/day)/ MOE (g)	Short-Term Residential Exposure (mg/kg/day)/ MOE		Short-Term Residential Exposure (mg/kg/day)/ MOE		Dermal	Inhalation	Oral and/or Dermal (excludes TM dermal exposure)
		Oral TM/ MBC	Dermal TM (b)		Oral (a, g)	Dermal (b)	Dermal (b)	Inhalation (d)			
Children (1-6 years)	0.000262 MOE= 38,000 (9BW and FC)	0.36 (f) MOE = 27 (9BW and FC)	1.2 (0.084 absorbed) MOE = 81 (9BW and FC) (TM)	0.000501 MOE = 20,000 (9BW and FC)	0.0116 (f) MOE =860 (9BW and FC)	0.049 (0.0017 absorbed) MOE = 5,900 (developmental)	NA	NA	5,900 (MBC only; developmental) **81 (TM only, 9BW and FC)**	NA	**26 (9BW and FC)** **(Recalc)**
Children (7-12 years)	0.000171 MOE= 58,000 (9BW and FC)	NE	0.21 (0.0147 absorbed) (e) MOE = 470 (9BW and FC) (TM)	0.000294 MOE = 34,000 (9BW and FC)	none	0.026 (0.00091 absorbed) (e) MOE= 11,000 (developmental)	NA	NA	470 (TM only; 9BW and FC) 11,000 (MBC only; developmental)	NA	17,000 (9BW and FC) **(recalc)**
Females 13-50 yrs	0.000075 MOE = 130,000 (9BW and FC/ development-al)	NE	2.42 (0.17 absorbed) (e) MOE =41 (9BW and FC)	0.00012 MOE= 83,000 (9BW and FC/develop-mental)	none	0.381 (0.0134 absorbed) (e) MOE =750 (developmental)	0.457 (0.016 absorbed) MOE = 620 (develop-mental)	0.0042 MOE = 230 (respira-tory)	**41 (TM only; 9BW and FC)**	**230 (respira-tory)**	**610 (TM and MBC uses)**

TM = Thiophanate-methyl
NE = not evaluated.
BW = body weight

FC= food consumption

(a) MOE for thiophanate-methyl, as MBC equivalents, calculated based on the MBC toxicity endpoints: short-term oral NOAEL of 10 mg/kg/day for decreased body weight and food consumption. Thiophanate-methyl converted to MBC equivalents based on the TEF approach, with TEFs of 1 for all populations since the short-term oral endpoint for thiophanate methyl is used to assess MBC short-term oral exposures.

(b) For dermal thiophanate-methyl exposures, the dermal NOAEL of 100 mg/kg/day based on decreased body weight and food consumption was used to assess dermal exposures to both children and females 13-50 yrs. For MBC dermal exposure, the oral NOAEL of 10 mg/kg/day based on developmental effects was used to assess dermal exposure to children and females 13-50 yrs. Dermal exposure adjusted for 3.5% dermal absorption factor for MBC and 7% for TM to estimate absorbed doses.

(c) Sum of MOEs for MBC. For children, TM dietary exposures not added since acute oral endpoint is based on tremors. For females 13-50, inhalation MOE was not aggregated with oral and dermal MOEs because the endpoint (respiratory effects) is different than the dermal and oral NOAEL based on developmental effects.

(d) Inhalation NOAEL of 0.96 mg/kg/day, based on respiratory effects, was used to assess MBC inhalation exposure.

(e) For children 7-12 years, dermal exposure from harvesting fruit, which has highest dermal exposure. For females 13-50 yrs, dermal exposure from harvesting fruit and dermal lawn contact, in addition to broadcast application of liquid lawn treatment (handler exposure). Postapplication dermal exposure from mowing lawns and golfing were approximately an order of magnitude lower.

(f) For thiophanate-methyl includes turf mouthing, hand to mouth, and incidental soil ingestion for lawns treated with liquid formulation at 19.3 lb ai/acre, which result in higher exposures than granular treatments at 11 lb ai/acre. Thiophanate-methyl converted to MBC equivalents based on the TEF approach, with TEF of 1used since the short-term oral endpoint for thiophanate methyl is used to assess MBC short-term oral exposures. For MBC, includes turf mouthing and hand to mouth activity only. This excludes the incidental granular ingestion scenario, which is considered to be an episodic event.

(g) MOE based on short-term oral endpoint of 10 mg/kg/day for decreased body weight and food consumption.

Table 13
Aggregate MBC DWLOCs for Short-Term Exposures
Aggregate 2: MBC From All Uses

Population Subgroup	NOAEL or LOAEL (mg/kg/day)	Target MOE	Maximum Exposure (MBC Acute PAD) (mg/kg/day)	MBC Average Chronic Food Exposure (mg/kg/day) (a)	Residential Exposure (as MBC Equivalents) (mg/kg/day) (b)	Potential MBC Max. Water Exposure (mg/kg/day) (c)	Long-Term MBC Surface Water EEC (Fg/L)	Long-term MBC Ground Water EEC SCI-GROW (Fg/L)	Short-Term MBC DWLOC (Fg/L) (d,e,f)
Children (1-6 years)	10	1000	0.01	0.000763	0.37	None (no room)	50 to 243	0.51 to 15	Zero (No room)
Children (7-12 years)	10	1000	0.01	0.000465	None (h)	0.00954			95
Females (13-50 years)	10	1000	0.01	0.000195	0.016 (g)	None (no room)			Zero (No room)

TM = thiophanate-methyl

(a) Values from Table 12 represent the sum of MBC dietary exposure from Thiophante methyl use. Includes thiophanate-methyl dietary exposure (as MBC equivalents) (i.e., for children 1-6 years, 0.000262 + 0.000501 = 0.000763 mg/kg/day).

(b) Values based on oral MBC and TM (as MBC equivalent) exposures from lawn use. Excludes dermal MBC and TM exposure because MBC and TM dermal endpoints are based on different effects (i.e., developmental effects for MBC and decreased body weight and food consumption for TM), therefore, a TEF approach could not be used to adjust TM exposures into MBC equivalents. For females, absorbed dermal exposure from MBC paint application was used to calculate DWLOC since this exposure is higher than dermal exposure from thiophanate-methyl uses. Inhalation exposures were not included because of a different toxicity endpoint (respiratory effects).

(c) Potential maximum water exposure (mg/kg/day) = Acute PAD (mg/kg/day) - [Chronic Food Exposure + short-term Residential Exposure (mg/kg/day)]. Includes MBC residential exposure from Thiophante Methyl use for children or MBC as a paint additive for females.

(d) DWLOC (Fg/L) = Maximum water exposure (mg/kg/day) x body wt (kg) ÷ [(10^{-3} mg/Fg) x water consumed daily (L/day)].

(e) HED default body weights are: adult females, 60 kg; and children, 10 kg for children.

(f) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.

(g) Based on MBC exposures as a paint additive and excludes residential exposure from TM uses (which were much lower than paint exposures).

(h) Excludes dermal TM and MBC exposure. MBC and TM dermal endpoints are based on different toxicological endpoints, therefore, TM exposures were not converted to MBC equivalents. MBC dermal exposure excluded because endpoint (developmental effects) differs from the short-term oral endpoint (decreased body weight and food consumption).

5.3 Intermediate-Term Aggregate Risk

5.3.1 Aggregate 1: Thiophanate-methyl and MBC (from Thiophanate-methyl Uses)

Intermediate-term aggregate risk estimates were not conducted for thiophanate-methyl and MBC because most of the intermediate-term residential post application exposures for children playing on treated lawns result in MOEs less than 300 for thiophanate-methyl, and therefore already exceed HED's level of concern based on a screening-level assessment using the residential SOPs. Any additional intermediate-term-term exposures through food and drinking water would result in MOEs that would further exceed HED's level of concern.

As shown on Table 10, intermediate-term dermal post application MOEs for thiophanate-methyl alone range from 780-1,800 for harvesting fruit, and 540-940 for dermal contact with treated turf by young children. MOEs for incidental ingestion of thiophanate-methyl residues on treated turf were also of concern and ranged from 9 to 240, except incidental soil ingestion for which MOEs were > 1000. The thiophanate-methyl dermal and oral intermediate-term aggregate MOEs for a child (1-6 years) playing on a treated lawn ranges from 27 to 46. The postapplication MOEs for mowing treated turf and golfing are above 300 and do not exceed HED's level of concern. The MOEs for MBC resulting from post application exposures are all above 1000, except for hand to mouth activity by children (MOE=910) and therefore, do not exceed HED's level of concern, but do contribute to further overall exposures of concern.

5.3.2 Aggregate 2: Thiophanate-methyl and MBC from All Uses

As discussed for the intermediate-term aggregate 1 assessment, several of the intermediate-term residential post application exposures for children playing on treated lawns result in MOEs less than 300 for thiophanate-methyl uses alone, and therefore already exceed HED's level of concern based on a screening-level assessment using the residential SOPs. Therefore, any additional intermediate-term-term exposures through food and drinking water would result in MOEs that would further exceed HED's level of concern. Consequently, an aggregate assessment for thiophanate-methyl and MBC from all uses was not conducted.

5.4 Chronic Non-Cancer and Cancer Aggregate Risk

The chronic aggregate risk estimate for thiophanate-methyl and MBC addresses exposure from food and water. For the Tier III chronic dietary exposure analysis, field trial data and tolerance level residues, in conjunction with percent crop treated data were used to assess dietary exposures.

5.4.1 Aggregate 1: Thiophanate-methyl and MBC (from Thiophanate-methyl Use)

5.4.1.1 Aggregate Chronic Non-Cancer and Cancer Risk Assessment

Non-Cancer Aggregate

The thiophanate-methyl chronic noncancer dietary risk estimates range is less than 1.2% of the cPAD for thiophanate-methyl, with infants (< 1 yrs) being the highest exposed population subgroup (1.2%

of the cPAD). For MBC, the chronic noncancer dietary risk estimates range from 0.7% to 20%, with highest risk estimates for children 1-6 years (20% of the cPAD). Thus, the chronic dietary (food) risk estimate associated with thiophanate-methyl or MBC exposure individually is below the Agency's level of concern.

Because thiophanate-methyl and MBC have common chronic toxicity (liver effects), and because individuals are likely to consume both chemical residues on thiophanate-methyl-treated commodities, it is appropriate to add thiophanate-methyl and MBC chronic dietary risk estimates. Although the chronic PAD for thiophanate-methyl is based specifically on thyroid effects, the liver is a target organ of this chemical and the cancer effects are based on mouse liver tumors. The aggregate chronic dietary risk estimates include exposure to thiophanate-methyl and MBC residues in food and water; there are no thiophanate-methyl uses that could result in chronic residential exposure. Average chronic dietary food risk estimates are below the Agency's level of concern. The total dietary exposure to thiophanate-methyl and MBC for the highest exposed population subgroup, children 1-6 years, is 21% of the cPAD for liver/thyroid effects, leaving 79% of the cPAD available for exposure through drinking water. As noted previously, all thiophanate-methyl dietary exposures were converted to MBC equivalents using the TEF approach. The DWLOCs were then estimated using the cPAD for MBC.

Cancer Aggregate

The cancer aggregate risk estimate also includes chronic dietary exposures from thiophanate-methyl and MBC residues estimated in food and water, and from residential uses of thiophanate-methyl, because both chemicals cause mouse liver tumors. Total thiophanate-methyl and MBC dietary cancer risk estimate is $2x10^{-6}$ for a 70 year exposure to the general U.S. population based on a refined Tier 3 dietary exposure analysis. This cancer risk estimate exceeds HED's level of concern of $1x10^{-6}$ for the general population. In addition, cancer risk estimates associated with some residential uses of thiophanate-methyl also exceed HED's level of concern (i.e., handler risks are $3.2x10^{-6}$ for hand application of granules to ornamentals, while post application cancer risks of concern are $1.2x10^{-6}$ to $3.7x10^{-6}$ for harvesting fruit and dermal contact with treated lawns the day of treatment).

5.4.1.2 Chronic Non-Cancer and Cancer DWLOC Calculations

As noted previously, all thiophanate-methyl dietary exposures were converted to MBC equivalents using the TEF approach. The DWLOCs were then estimated using the cPAD for MBC and by combining the average dietary exposure as MBC equivalents.

The chronic non-cancer DWLOC values are presented in Table 14. For each population subgroup listed, the chronic PAD and the chronic dietary (food) exposure (from Table 7) for that subgroup were used to calculate the chronic DWLOC for the subgroup, using the formulas in footnotes of Table 14. Note that under the cancer risk assessment that DWLOC values for cancer effects are effectively zero because chronic dietary exposure to thiophanate-methyl and MBC residues on food alone exceed HED's level of concern for cancer ($>1x10^{-6}$). Consequently, any additional water exposure will further contribute to potential exposures of concern.

Using conservative screening-level models, the estimated long-term concentrations of MBC in groundwater (SCI-GROW) range from 0.51 to 15 Fg/L, while surface water EECs range from 50 to

243 Fg/L depending on whether ornamentals, turf or onions are treated. The estimated long-term concentrations of thiophanate-methyl in groundwater (SCI-GROW) range from 0.006 to 0.17 Fg/L, while the surface water EECs range from 0.44 to 367 Fg/L depending on use pattern. As noted previously, thiophanate-methyl degrades to MBC in water within a few days.

As shown on Table 14, the non-cancer DWLOCs are below most of the surface water EECs for MBC for children and females (13-50 years). The DWLOCs for children and females (13-50 years) range from 20 to 71 Fg/L, which are less than the MBC EECs for surface water of 243 Fg/L for ornamental use, and 73.5 Fg/L for onion use. However, the DWLOCs are greater than the surface water EEC resulting from turf use of 50 Fg/L and the groundwater EECs of 0.51 to 15 Fg/L. As noted previously, when EECs are **less** than DWLOCs, HED considers the aggregate risk [from food + water] to not exceed HED's level of concern. Only the MBC EECs are used in this aggregate assessment, although the thiophanate-methyl EECs are shown for comparison purposes because individuals may be exposed to both thiophanate-methyl and MBC simultaneously in drinking water. Therefore, HED concludes with reasonable certainty that **chronic (non-cancer) and cancer aggregate exposure to thiophanate-methyl and MBC (from thiophanate-methyl use) exceeds the HED's level of concern.**

However, it should be noted that the EECs do not reflect dilution from source to tap nor do they reflect water treatment. HED also notes that the concentration estimate for long-term concentrations of thiophanate-methyl and MBC in surface water from GENEEC (from ornamental and turf uses) represents a 56-day average number only, and not an annual average concentration (which is appropriate for use in chronic assessments), nor a multi-year mean (which is appropriate for use in cancer assessments). Although HED divides this 56-day average concentration by a factor of 3, the resulting concentration value may not represent a long-term concentration value and should be refined for chronic/cancer assessments.

The surface water EEC of 73.3 Fg/L for MBC from onion use is a 36-year average based on one application per year using the Tier 2 PRZM/EXAMS model, and therefore is a more refined value.

Table 14
DWLOCs for Chronic Non-Cancer and Cancer Aggregate Dietary Exposure
Aggregate 1: Thiophanate-methyl and MBC (from Thiophanate-methyl Use)

Population Subgroup (a)	MBC Chronic PAD (mg/kg/day)	MBC Q_1* $(mg/kg/day)^{-1}$	Total Chronic Food Exposure as MBC Equivalents (mg/kg/day) (b)	Max. Water Exposure (mg/kg/day (c)	Surface Water (Fg/L)	Ground Water SCI-GROW (Fg/L)	Chronic MBC DWLOC (Fg/L) (d,e,f)
Non-Cancer							
U.S. Population	0.025	2.39×10^{-3}	0.000792	0.0242	MBC: 50 (turf) 73.5 (onions) 243 (ornamentals) TM: 0.44 (onions) 73.3 (turf) 367 (ornamentals)	MBC: 0.51 (onions) 3 (turf) 15 (ornamentals) TM: 0.006 (onions) 0.033 (turf) 0.17 (ornamentals)	850
All Infants (< 1 Year)	0.0025		0.000373	0.00213			21
Children (1-6 years)			0.000526	0.00197			20
Females (13-50 years)			0.000127	0.00237			71
Cancer							
U.S. Population	NR	2.39×10^{-3}	0.000792	No room (g)			zero (g)

NR=not relevant

(a) In addition to the U.S. population (all seasons), the most highly exposed subgroup within each of the infants, children, female groups is listed.

(b) Values are from Table 7, and represent the sum of thiophanate-methyl and MBC dietary exposure. Thiophanate-methyl values were converted to MBC equivalents using the TEF approach.

C) Maximum Water Exposure (mg/kg/day) (non-cancer) = Chronic PAD (mg/kg/day) - [Chronic Food Exposure (mg/kg/day) Maximum water exposure (cancer) = (1x10-6/Q1*) - chronic food exposure. Thiophanate-methyl has no registered residential uses expected to result in long-term exposure

(d) DWLOC (Fg/L) = Maximum water exposure (mg/kg/day) x body wt (kg) ÷ [(10^{-3} mg/Fg) x water consumed daily (L/day)].

(e) HED default body weights are: general U.S. population, 70 kg; adult females, 60 kg; and infants/children, 10 kg.

(f) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.

(g) Dietary risk alone exceeds HED's level of concern.

5.4.2 Aggregate 2: Thiophanate-methyl and MBC From All Uses

5.4.2.1 Aggregate Chronic Non-Cancer and Cancer Risk Assessment

Chronic aggregate exposure includes all MBC chronic dietary exposure resulting from registered uses of thiophanate-methyl. In addition, thiophanate-methyl and MBC have the same toxic effects (i.e., liver effects) and therefore were added together. Chronic residential exposures to MBC are not anticipated based on registered uses for thiophanate-methyl. While there are potentially chronic inhalation exposures to MBC vapors from use of MBC as a paint additive, these exposures were not considered in the non-cancer aggregate assessment because the endpoint of concern (respiratory effects) is different from the chronic oral endpoint of concern (liver effects). However, these potential chronic inhalation exposures are assessed in the cancer aggregate assessment below.

Non-Cancer Aggregate

The Aggregate 2 assessment is identical to the Aggregate 1 assessment for non-cancer effects because all benomyl food uses were recently proposed for cancellation by the benomyl registrant in April 2001. Therefore, the chronic non-cancer Aggregate 2 assessment includes chronic exposures to thiophanate-methyl and MBC in food and drinking water through thiophante-methyl uses.

Cancer Aggregate

For this assessment, HED evaluated the aggregate exposures to MBC resulting from registered uses of thiophanate-methyl and MBC. Chronic aggregate cancer exposure, includes all MBC chronic dietary exposure resulting from both thiophanate-methyl and MBC. In addition, thiophanate-methyl and MBC have the same toxic effects (i.e., liver effects), both have Q_1*s based on mouse liver tumors, and therefore were added together. Chronic residential exposures to MBC are not anticipated based on registered uses for thiophante methyl. There are potential chronic inhalation exposures to MBC from MBC's registered use as a paint additive (i.e., dermal and inhalation exposures to a resident painter, and chronic inhalation to vapors in a painted room). Therefore, these MBC inhalation exposures were included in the aggregate risk estimates.

As shown on Table 15 the aggregate cancer dietary risk estimates (food only) for MBC and thiophanate-methyl, combined is $2x10^{-6}$. In addition, the total cancer risk estimates for thiophanate-methyl from dietary and some residential uses is $9x10^{-6}$. The combined cancer risk estimate for combined thiophanate-methyl and MBC exposures from dietary and selected residential uses (i.e., lawn treatment and postapplication exposure) is $1x10^{-5}$, primarily because of the residential exposures to thiophanate-methyl. These risk estimates exceed HED's level of concern.

5.4.2.2 Chronic Cancer DWLOC Calculations

As noted previously, all thiophanate-methyl dietary exposures were converted to MBC equivalents using the TEF approach. The DWLOCs were then estimated using the Q_1* for MBC and by combining the average dietary exposure as MBC equivalents.

As shown on Table 15 the aggregate cancer dietary risk estimates (food only) for MBC and thiophanate-methyl, combined is $2x10^{-6}$, while combined food and residential exposures result in cancer risks as high as $1x10^{-5}$. Therefore, the cancer **DWLOC is effectively zero** because any additional contribution from water will only further contribute to exposures of potential concern. Therefore, **the aggregate exposure to thiophanate-methyl and MBC from all uses on food, residential settings, in addition to potential residues in water exceeds HED's level of concern for carcinogenic effects.** The cancer risk estimates for MBC use as a paint additive are conservative, because they are based on high end assumptions for occupancy, air exchange rates used in the air model, and assume no degradation or matrix effects of the paint.

Therefore, HED concludes the aggregate exposure to thiophanate-methyl and MBC from all food and residential uses, as well as potential residues in water exceeds HED's level of concern for carcinogenic effects.

As noted previously, the EECs do not reflect dilution from source to tap nor do they reflect water treatment. HED also notes that the concentration estimate for long-term concentrations of MBC in surface water from GENEEC represents a 56-day average number only, and not an annual average concentration (which is appropriate for use in chronic assessments), nor a multi-year mean (which is appropriate for use in cancer assessments). Although HED divides this 56-day average concentration by a factor of 3, the resulting concentration value may not represent a long-term concentration value and should be refined for chronic/cancer assessments. The surface water EEC of 73.3 Fg/L for MBC from onion use is a 36-year average based on one application per year using the Tier 2 PRZM/EXAMS model, and therefore is a more refined value.

Table 15 Aggregate 2: Summary of Aggregate Cancer Risk Estimates Thiophanate-methyl and MBC Tier 3 Chronic Dietary Exposure Analysis by DEEM (Excludes Water)							
Population Subgroup (a)	**Thiophanate-Methyl as MBC equivalents**		**MBC +other metabolites (from Thiophante Methyl)**		**MBC (from MBC Use as Paint Additive)**		**Total Thiophanate-Methyl and MBC**
	Exposure (mg/kg BW/day) (d)	**Lifetime Cancer Risk Estimate (a)**	**Exposure (mg/kg BW/day)**	**Lifetime Cancer Risk Estimate (a)**	**Exposure (mg/kg BW/day) (c)**	**Lifetime Cancer Risk Estimate (a)**	**Lifetime Cancer Risk Estimate (b)**
US Population							
Diet	0.000629	**1.5×10^{-6}**	0.000163	3.9×10^{-7}	None		**2×10^{-6}**
Residential	0.0033 (f)	**7.8×10^{-6}**	0.00036 (e)	8.6×10^{-8}	9×10^{-5}	2.2×10^{-7}	
Total		**9×10^{-6}**		5×10^{-7}		2.2×10^{-7}	**1×10^{-5}** (TM use) **2×10^{-6}** (TM and MBC use, excluding TM residential use)

(a) Lifetime cancer risk = Dietary Exposure x Q1*, where Q1* is 2.39×10^{-3} $(mg/kg/day)^{-1}$ for MBC and 1.38×10^{-2} $(mg/kg/day)^{-1}$ for thiophanate-methyl.
(b) Total cancer risk is the sum of cancer risks from thiophanate-methyl and MBC.
(c) Sum of exposure to both residential handler during paint activities and to vapors following painting.
(d) Dietary thiophanate-methyl exposure adjusted by a TEF of 5.77 based on differences in the Q1* potency estimates for thiophanate-methyl and MBC.
(e) Exposure based on harvesting fruit, which has highest MBC exposure.
(f) Thiophanate-methyl exposure based on broadcast lawn treatment (0.00032 mg/kg/day) and dermal postapplication lawn exposure (0.000246 mg/kg/day), with an adjustment for TEF (i.e., multiplied by 5.77) to convert to MBC equivalents.

Table 16
Aggregate 2: Aggregate MBC DWLOCs for Chronic Exposures
Thiophanate-Methyl and MBC (all uses)

Population Subgroup	MBC Chronic PAD (mg/kg/ day)	Q1* $(mg/kg/day)^{-1}$	MBC Chronic Average Food Exposure (mg/kg/day) (a)	Total Food as MBC Equivalents (mg/kg/day)	MBC Equivalents (from Thiophanate-Methyl Residential Use)	MBC (from MBC as Paint Additive) (mg/kg/day)	Potential MBC Max. Water Exposure (mg/kg/day) (b)	MBC Long-Term Surface Water EEC (Fg/L)	MBC Long-term Ground Water EEC SCI-GROW (Fg/L)	Chronic DWLOC (Fg/L) (c,d,e)
Non-Cancer (Same as Aggregate 1)										
Cancer										
US Population	0.025	$2.39x10^{-3}$	0.000254	0.000792 (i)	0.0019 (f)	0.00009 (h)	Zero	MBC from TM use: 50 (turf) 73.5 (onions) 243 (ornamentals)	MBC from TM use: 0.51 (onions) 3 (turf) 15 (ornamentals)	Zero

NA = not applicable.
(a) Exposure from Table 15 for cancer exposure estimates.
(b) Non-cancer Maximum Water Exposure (mg/kg/day) = cPAD (mg/kg/day) - [Chronic Food Exposure]. Cancer Maximum Water Exposure (mg/kg/day) = $(1x10^{-6} / Q_1*)$ - [Chronic Food Exposure+ residential exposures]. MBC Cancer water exposure estimate also incorporates thiophanate-methyl because MBC and thiophanate-methyl Q1*s are both based on mouse liver tumors, and both are present on the same food
(c) DWLOC (Fg/L) = Maximum water exposure (mg/kg/day) x body wt (kg) ÷ [$(10^{-3}$ mg/Fg) x water consumed daily (L/day)].
(d) HED default body weights are: general U.S. population, 70 kg; adult females, 60 kg; and infants/children, 10 kg.
(e) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.
(f) Based on harvesting fruit treated with thiophanate-methyl.
(g) MBC inhalation exposure not considered for non-cancer because the toxicity endpoint (respiratory effects) differs from the oral endpoint.
(h) Sum of exposure to both residential handler during paint activities and to vapors following painting.
(i) Cancer dietary exposure from Table 15, which is the sum of total thiophanate-methyl and MBC exposure (as MBC equivalents).

6.0 CUMULATIVE EXPOSURE AND RISKS

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

EPA does not have, at this, time, available data to determine whether thiophanate-methyl has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For purposes of this reregistration decision, EPA has assumed that thiophanate-methyl does not have a common mechanism of toxicity with other substances.

On this basis, the registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether thiophanate-methyl shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for thiophanate-methyl need to be modified or revoked.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on June 30, 2000 (65 FR 40644-40650) and is available from the OPP Website at: http://www.epa.gov/fedrgstr/EPA-PEST/2000/June/Day-30/6049.pdf
In the draft guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed. The proposed guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity is expected to be finalized by the summer of 2001.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "*Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*" (64 FR 5795-5796, February 5, 1999).

HED did not perform a cumulative risk assessment as part of this reregistration review for thiophanate-methyl because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of thiophanate-methyl. If HED identifies other substances that share a common mechanism of toxicity with thiophanate-methyl, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment once the final guidance HED will use for conducting cumulative risk assessments is available.

It is possible that thiophanate-methyl and MBC may express toxicity and carcinogenicity through a common mechanism as the other benzimidazole compounds and, consequently these pesticides may be considered as a group when performing cumulative risk assessments in the future. It is also noted that both thiophanate-methyl and MBC are structurally related to several other benzimidazole compounds (primarily veterinary drugs) that are suspect carcinogens including albendazole, fenbendazole, mebendazole, oxfendazole and thiabendazole. Most of the benzimidazole compounds are regulated by the Center for Veterinary Medicine, Food and Drug Administration (FDA) as animal drugs. The potential carcinogenic effects of these compounds were reviewed by the Center for Veterinary Medicine, Food and Drug Administration (FDA). Thiabendazole also has agricultural uses.

7.0 OCCUPATIONAL EXPOSURE

Thiophanate-methyl ([1,2-phenylene)-bis(iminocarbonothioyl)]bis[carbamate]) is a systemic fungicide registered for use in a wide variety of agricultural, ornamental, and residential settings. There are 36 active registrations and 22 special local need registrations. Major food/feed crops include: almonds, apples, dry beans, green beans, peaches, potatoes (seed pieces), soybeans, sugar beets and wheat. Non-agricultural uses include ornamentals, turf (sod farms, residential and recreational lawns), greenhouses, interior scapes, landscaping, and nursery use including seedling and bulb treatment. Grapes and pears have been included in this section due to currently pending petitions. Thiophanate-methyl is applied by most ground and aerial methods, and also applied as a seed or seed piece treatment in dry or slurry form and a dip treatment for seeds. There is a potential for exposure from agricultural, commercial operator, and residential uses.

Thiophanate-methyl is formulated as a wettable powder (WP), water-dispersible granules (WDG), flowable concentrate (FC), emulsifiable concentrate (EC), granular (G), and ready-to-use liquid ranging from 1.65% to 90% active ingredient.

Occupational exposures to thiophanate-methyl can occur during pesticide handling (mixing, loading and application activities) or post-application work. Because environmental fate data suggest that thiophanate-methyl converts to MBC, postapplication exposures were assessed for both thiophanate-methyl and MBC residues. Occupational postapplication exposure can occur for agricultural workers during scouting, irrigation, cultivation, harvesting and handling seeds and seedlings. Details of the occupational exposure assessment are presented in the attached memorandum from G. Bangs to D. Smegal D271922, March 15, 2001.

7.1 Occupational Handler

Exposure Scenarios

Based on the registered use patterns, HED has identified 25 major exposure scenarios for which there is potential occupational handler exposure during mixing, loading, and applying products containing thiophanate-methyl to agricultural crops and turf/ornamentals. These scenarios are as follows:

(1) mixing/loading wettable powders for: (a) aerial/chemigation, (b) groundboom, (c) airblast, (d) lawn handgun, and (e) dip application;
(2) mixing/loading dry flowable/WDG for: (a) aerial/chemigation, (b) groundboom, (c) airblast, (d) lawn handgun, and (e) dip application;
(3) mixing/loading liquid flowable concentrates for: (a) aerial/chemigation, (b) groundboom, (c) airblast, (d) lawn handgun, and (e) dip application;

(4) loading granular formulations for: (a) aerial and (b) mechanical ground application for turf, and ornamental broadcast;
(5) loading dusts for seed treatment;
(6) applying sprays aerially;
(7) applying granulars aerially;
(8) applying sprays to crops with a groundboom sprayer;
(9) applying sprays with an airblast sprayer;
(10) applying sprays with a handgun sprayer;
(11) applying granular products to turf with tractor-drawn spreader;
(12) applying dip treatments;
(13) applying dust as a potato seed treatment;
(14) mixing/loading/applying liquids using a high pressure handwand;
(15) mixing/loading/applying wettable powder using a low pressure handwand;
(16) mixing/loading/applying liquids using a low pressure handwand;
(17) mixing/loading/applying dry flowables using a low pressure handwand;
(18) mixing/loading/applying with a backpack sprayer;
(19) mixing/loading/applying: (a) liquids, (b) dry flowables (WDG), and (c) wettable powders using a handgun sprayer;
(20) loading/applying granules to turf and ornamentals using a belly grinder;
(21) loading/applying granules to turf using a push-type spreader;
(22) loading/applying dust as a seed treatment (dry) in planter box (i.e., peanuts);
(23) loading/applying wettable powder/DF solution as a seedling or bulb dip treatment;
(24) flagging aerial spray applications; and
(25) flagging aerial granular applications.

These occupational scenarios reflect a broad range of application equipment, application methods and use sites. There are currently insufficient data to evaluate scenarios:12 (applying dip treatments), 17 (mixing/loading/applying dry flowables using a low pressure handwand) and 23 (loading/applying wettable powder/DF solution as a seedling or bulb dip treatment). Although there are no data to assess scenario 17, HED believes exposure resulting from this registered use scenario would be less than scenario 15 (i.e., mixing/loading/applying wettable powder using a low pressure handwand). Additional data are requested for the registered uses of scenarios 12 and 23. The crops on which thiophanate-methyl is used, and application rates are summarized below for the different thiophanate-methyl formulations. The application rate ranges reflect maximum single-treatment rates for various crops or groups of crops.

For the agricultural handlers, the estimated exposures initially are assessed assuming handlers are using baseline attire (i.e., long-sleeve shirt, long pants, shoes, and socks). If risk estimates exceed the level of concern for a given scenario with baseline attire, then risks are assessed with the addition of personal protective equipment (i.e., chemical-resistant gloves, double-layer body protection, and/or a respirator) as required. In general, the Agency uses the least PPE necessary to achieve risk estimates that do not exceed the level of concern. Also, if the risk estimates for *inhalation* exposures result in a MOE that is at least two-fold greater than the target MOE (i.e., MOE $ 200) at baseline (no respirator), then the inhalation exposures will not contribute significantly to an aggregate (dermal + inhalation) MOE. Therefore, addition of PPE, a respirator, is not warranted for that scenario. If the risk estimates exceed the Agency's level of concern (i.e., if MOE < 100) for a given scenario even with the addition of PPE, then the risks are assessed with the use of engineering controls (i.e., closed system mixing/loading and enclosed cabs or cockpits for applying and flagging).

Exposure Data Sources and Assumptions

No chemical-specific data on handler exposure were submitted to the Agency for thiophanate-methyl. Therefore, potential exposures resulting from handling and applying thiophanate-methyl were estimated using data from the Pesticide Handlers Exposure Database (PHED) Version 1.1. PHED is a software system consisting of two parts -- a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates). While data from PHED provides the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. For example, the agricultural groundboom scenario data in PHED may overestimate exposure from golf course ground application methods.

Occupational and Residential Exposure Task Force (ORETF) data were used to assess scenarios 19a, b and c, (mixing/loading/applying liquid, dry flowables or wettable powders using a handgun sprayer) and 21 (loading/applying granules to turf using a push-type spreader) (MRID 44972201). Scientific literature data were used to assess scenarios 5 (loading dusts), and 13 (applying dusts as a potato seed treatment) and 22 [loading/applying dust as a seed treatment (dry) in a planter box].

Potential exposures were calculated using unit exposures from PHED, ORETF or literature studies, multiplied by the amount of thiophanate-methyl handled per day (i.e., lb ai/day). The amount of thiophanate-methyl assumed handled per day was derived from the various application rates and the number of acres (or gallons of spray solution) that could be applied in a single day. Cancer risks were estimated only for the typical application rate, in accordance with HED policy.

The duration of exposure is expected to be short-, and intermediate-term for occupational handlers. The exposure duration for short-term assessments is 1 to 7 days, while intermediate-term durations are 1 week to 6 months. Maximum application rates were used to assess non-cancer exposure and risks, while the typical application rate was used to assess cancer risks. The standard default body weight of 70 kg was used to assess non-cancer and cancer effects, respectively.

Cancer risks were estimated for the various handler scenarios using two categories of handlers: private and commercial. “Private” handlers are assumed to mix, load, apply, or otherwise handle thiophanate-methyl as part of their duties on a single agricultural establishment of a typical size. “Commercial” handlers are assumed to be either custom “for-hire” applicators or individuals who handle thiophanate-methyl on a very large agricultural establishment. The Agency assumes that private handlers would handle thiophanate-methyl less frequently than commercial handlers. Except where specific information is available (such as greenhouses and golf courses), commercial handlers are assumed to handle thiophanate-methyl ten days for each one day that private handlers are assumed to handle it. Most private and commercial applicators were assumed to apply thiophanate-methyl 3 and 30 days/year, respectively for 35 years for most crops. When available, EPA used the average or “typical” application rate for assessing cancer risks, since the assessment is based on a lifetime of exposure.

Handler Risk Characterization

A summary of the short- and intermediate-term risk estimates for baseline, PPE and engineering controls is presented in Table 17 for agricultural and commercial uses. Table 17 also provides a summary of the crop-specific application rates assessed for thiophanate-methyl. As noted previously, only exposures to thiophanate-methyl were assessed for occupational handlers. Handlers are not expected to be exposed to MBC, because MBC is formed during the environmental degradation of thiophanate-methyl.

Non-cancer risk estimates are expressed in terms of the Margin of Exposure (MOE). MOEs for occupational handlers were derived by dividing appropriate NOAEL for thiophanate-methyl, shown on Table 3, by the daily dermal or inhalation exposure estimate. As noted previously, the short- and intermediate-term dermal NOAEL is 100 mg/kg/day from a 21 day dermal study in rabbits that observed decreased body weight and food consumption. The short and intermediate-term NOAEL of 10 mg/kg/day from an oral developmental study in rabbits was used to evaluate inhalation exposures to thiophanate-methyl, assuming inhalation and oral absorption are equivalent (i.e., 100% factor). The inhalation endpoint is also based on decreased body weight and food consumption, therefore, it is appropriate to combine dermal and inhalation exposure and risk estimates. Thiophanate-methyl is also classified as a possible human carcinogen (class C) based on the presence of liver tumors in mice following dietary exposure. The oral Q_1^* for thiophanate-methyl is 1.38 x 10^{-2} (mg/kg/day)$^{-1}$. This cancer potency factor was used to assess dermal and inhalation exposure to handlers. Because an oral Q_1* was selected, a 7% dermal absorption factor and 100% inhalation absorption factor (i.e., equivalent to oral absorption) were used.

For occupationally exposed workers, MOEs $100 (i.e., uncertainty factors of 10x for interspecies extrapolation and 10x for intraspecies variability) do not exceed HED's level of concern. MOEs below this level would represent a potential risk estimate of concern. As noted previously, a total dermal and inhalation MOE was calculated because the toxicity endpoint is identical for dermal and inhalation (decreased body weight and food consumption) exposures. Cancer risk estimates are presented as a probability of developing cancer. In general, the Agency is concerned whenever occupational cancer risk estimates exceed 1x10^{-4} and will attempt to mitigate cancer risk to workers to a lower level, preferably to 10^{-6} or less, by the addition of various exposure risk mitigation measures, where feasible.

The anticipated use patterns and current labeling indicate 25 major occupational handler exposure scenarios, which, when combined with typical ranges of application rates resulted in a total of 168 scenarios: 144 risk estimates for which PHED data were used, 12 risk estimates based on ORETF data, 3 major handler scenarios had no data (resulting in 6 evaluations), and 6 seed treatment uses for which published study data were used.

Noncancer Risk Estimates: The short- and intermediate-term noncancer risk estimates for dermal and inhalation exposures of occupational handlers at baseline attire, with the addition of PPE, and with the addition of engineering controls are summarized in Table 17. Overall, about half of the baseline exposure scenarios had MOEs $ 100; when maximum PPE were added, 90% of scenarios had MOEs $ 100, and all MOEs were greater than 100 when engineering controls were added, if feasible. Where data for baseline exposures were available, either from PHED, ORETF, or published literature, in general risk estimates did not exceed the level of concern (*except* when application rates exceed 10 lbs ai/acres) at baseline attire for:

C mixing and loading dry flowable formulations,
C loading granular formulations,

- applying with any equipment,
- mixing/loading/applying with any equipment, and
- flagging to support aerial applications.

For mixing and loading wettable powder formulations to support aerial or chemigation applications, engineering controls (i.e., water-soluble packaging) are required to achieve the target MOE for many crops and use patterns. For the remaining handler scenarios, in general risk estimates did not exceed the level of concern with the addition of PPE, *except* in a few instances when application rates exceed 10 lbs ai/acre. While the addition of gloves to baseline protection increased MOEs to $\geq$ 100 for most (83%) of scenarios, adding respirators and coveralls only increased the number of scenarios with MOEs $\geq$ 100 to 90%. The MOEs were less than 100 for the highest application rate for loader/applicators using push-spreaders and belly grinders, and no feasible engineering controls are available.

Cancer Risk Estimates: Table 17 summarizes the estimated cancer risks to private and commercial occupational handlers for each of the handler scenarios with baseline attire, with the addition of PPE, and with the addition of engineering controls. At baseline, most of the exposure scenarios had estimated cancer risks less than 10^{-4}, but greater than 10^{-6}. Cancer risk estimates at baseline for private and commercial handlers range from 9.4×10^{-4} to 3.1×10^{-9}, and from 9.4×10^{-3} to 9.2×10^{-9}, respectively. With the addition of PPE, cancer risk estimates for all private handler scenarios and most commercial handler scenarios were less than 10^{-4}. With PPE, cancer risk estimates for private and commercial handlers ranged from 1.2×10^{-8} to 5.5×10^{-5}, and from 1.4×10^{-8} to 5.5×10^{-4}, respectively. With the addition of engineering controls, where feasible, cancer risk estimates for all private handler scenarios were equal or less than 2.9×10^{-6}, and estimates for commercial applicators ranged from 1.1×10^{-7} to 2.9×10^{-5}. Handler scenarios with high application rates (greater than 10 lbs ai/acre), very high acreage crops (i.e., 1200 acres per day) or hand-held application equipment generally had cancer risk estimates greater than 10^{-6}, even with addition of PPE or engineering controls. Most hand application methods (hand-directed sprays, spreaders, etc.) do not have a practical means of enclosure or other engineering control.

As noted previously, there are insufficient information and data to adequately assess seed, seedling and dip applications. HED requests data for these registered uses.

The agricultural handler assessments are believed to be reasonable representations of thiophanate-methyl uses. There are, however, many uncertainties in these assessments. The uncertainties include but are not limited to the following:

- not all of the exposure data are of high confidence because of the lack of replicates and/or inadequate QA/QC in the studies

In particular, all hand application methods (wand, spreaders, belly grinder) are highly variable based on applicator techniques. These uncertainties are inherent in most pesticide exposure assessments. The handler assessments were based upon conservative assumptions (e.g., frequently maximum application rates, high daily acreage, 35-year exposure period) and therefore are believed to be protective of the handlers.

7.2 Postapplication

Exposure Scenarios

EPA has determined that there is potential exposure to persons entering treated sites (e.g., scouts and harvesters) after application is complete.

Postapplication Exposure Data and Assumptions

Most post-application worker exposures to thiophanate-methyl and MBC are assumed to be of short- (1-7 days) to intermediate-term (1 week to 6 months) duration, based on the available use data. Based on the slow dissipation rate of thiophanate-methyl seen in submitted studies, it is possible that some workers may be exposed over a period greater than 180 days per year. This is most likely to happen in an enclosed greenhouse situation, where residues decline slowest, or less commonly, in picking field crops such as strawberries. The average application rate based on surveys is once per season per crop, but labels allow repeated application when needed. In the agricultural fields, thiophanate-methyl slowly breaks down (hydrolyzes) to MBC in a period of days to weeks after application based on foliar residue dissipation data. The MBC residues remain lower than thiophanate-methyl throughout the dissipation period. All of the re-entry MOEs use thiophanate-methyl residues alone, as the highest detected MBC residues incurred an MOE of 250, and therefore does not exceed HED's level of concern.

Based on toxicological criteria and potential for exposure, HED has conducted a dermal exposure assessment for occupational postapplication exposure to thiophanate-methyl. Inhalation is not expected be a significant postapplication exposure route, based on the low chemical vapor pressure and outdoor dilution effects.

Post-application dislodgeable foliar residue (DFR) data were submitted for apples, strawberries, and cut flowers in a greenhouse, as well as transferable residues from treated turf. All of these data were used in this assessment along with HED standard transfer coefficients based on EPA Science Advisory Council for Exposure guidance (Policy 3.1 8/7/00) to assess potential exposures to workers reentering treated sites. For occupational exposures, an 8-hour exposure day was assumed. For assessing short- and intermediate-term exposures associated with non-cancer risks, the maximum application rate by crop is assumed, whereas, for assessing exposures associated with cancer risks, the typical application rate, if known, for a crop is assumed.

Risk estimates for short- and intermediate-term dermal exposures are assessed based on the DFR data on day 0 or day 1, whichever is greater. Cancer risk estimates are assessed based on the average DFR data in the range of day 1 to day 14, since in general, thiophanate-methyl can be reapplied at 14-day intervals. This means that if the restricted-entry interval were set at day 1, EPA estimates that workers would enter treated areas on days 1 through day 14, with the average exposure being the average of DFRs between days 1 and 14. If cancer risk estimates are of concern based on the average DFR between days 1 and 14, then risks are assessed using the average day 2 to day 14, day 3 to day 14, etc. This assesses the risks with increasing REIs. In some instances, risk estimates remain greater than 10^{-6} after day 14, which is the usual retreatment interval. In these cases, EPA back-calculated to ascertain what day of entry would achieve cancer risk estimates that were less than 10^{-6}. If the calculations indicate, for example, that cancer risk estimates reach 1.0×10^{-6} on day 30, that means that the *average* or *typical* day of entry is day 30 to reach that risk level. That should not be interpreted as an REI of 30 days, but rather is a range-finder calculation.

Postapplication Risk Characterization

The MOEs for postapplication workers were derived by dividing the appropriate NOAEL for thiophanate-methyl, shown on Table 3, by the daily dermal exposure estimate. As noted previously, the short and intermediate-term dermal NOAEL of 100 mg/kg/day for thiophanate-methyl is from a 21-day dermal study. For cancer, the oral Q_1^* for thiophanate-methyl is 1.38×10^{-2} $(mg/kg/day)^{-1}$. These cancer estimates were used to assess dermal exposure to postapplication workers. Because the Q1* is based on an oral study, a dermal absorption factor of 7% for thiophanate-methyl was applied to estimate the dermal cancer risks.

As noted previously, MOEs $100 do not exceed HED's level of concern for occupationally exposed workers. MOEs below this level would represent a potential risk concern. Only dermal exposures to thiophanate-methyl were assessed, as post-application inhalation exposure is expected to be negligible because inhalation exposures have been shown historically to account for negligible percentage of the overall body burden and the vapor pressure of thiophanate-methyl is low (1.3×10^{-5} mmHg). As stated above, MBC residues did not exceed the level of concern.

Postapplication Risk Estimates for thiophanate-methyl: Table 18 presents an overall summary of occupational postapplication risk estimates by crop and worker activity. The results of the short- and intermediate-term dermal postapplication assessments indicate that the MOEs were less than 100 for most tree crops, cut flowers/herbaceous ornamentals and some lawn-care activities at the current WPS-required restricted entry intervals (REIs) of 12 hours, and therefore exceed HED's level of concern. The REI represents the duration in days which must elapse before the Agency would not have a concern (MOE # 100) for a worker wearing a long-sleeved shirt and long pants to enter the treated area and perform specific tasks. The risk estimates were considerably higher when residue data from dry (western) versus humid (eastern) climates for apple trees, or from non-irrigated turf versus irrigated turf were used to predict worker risks. The risk estimates for tree crops generally attained an MOE of 100 within one week for most activities when NY data were used, while one to several months were required to attain an MOE of 100 when WA data were used to estimate risks for apples, peaches, grapes, and large ornamentals. High-contact activities on turf required 7 days to attain an MOE of 100 using non-irrigated turf data, but only 2 days using the irrigated turf data. Row crop reentry risk estimates using strawberry DFR data indicated 1 day was sufficient to achieve an MOE of 100 for most tasks, except working with ornamentals. These risk estimates are less certain for crops which do not resemble strawberry plants in architecture and leaf surface. Cut flowers risk estimates, using data for transfer coefficients and residues from thiophanate-methyl studies, showed MOEs of 100 were not attained until 1-2 months after application. Using 14 day average residues, cancer risk estimates for most activities on most crops were between 10^{-4} and 10^{-6}, although some high-contact activities exceeded 10^{-4}, notably those involving cut flowers and woody ornamentals.

Postapplication Risk Estimates for MBC: A worker post-application exposure scenario was also assessed for the metabolite of thiophanate-methyl, MBC. The same assumptions as for thiophanate-methyl were used along with the maximum MBC DFR for each study. The highest MBC DFR value was used because of the uncertainties in the percentage of thiophanate-methyl that degrades to MBC at any time in the environment, as well as the dissipation rate of MBC (which increases before decreasing after thiophanate-methyl application). The risk assessment indicates that noncancer risks to postapplication workers do not exceed the level of concern (MOE >100) from exposures to MBC residues as a degradate of thiophanate-methyl. For short-term risks, the MOEs range from 250 to 630,000 with a target of 100.

Cancer risk estimates range from 1.9×10^{-8} to 4.4×10^{-6}. Thiophanate-methyl residues alone were used to calculate the time required postapplication to achieve MOEs $\geq$100, as the highest detected MBC residues incurred an MOE of 250.

The occupational postapplication assessments are believed to be reasonable representations of thiophanate-methyl uses. While some individual's exposure may exceed these estimates, the Agency believes that most workers in each group would have fewer than 180 days of exposure than are assumed for the indicator crops. There are, however, many uncertainties in these assessments. The uncertainties include but are not limited to the following:

- not all of the exposure data are of high confidence because of the lack of replicates and/or inadequate QA/QC in the studies; and
- application timing in comparison to actual potential postapplication exposure scenarios.

These uncertainties are inherent in most pesticide exposure assessments. The conservative nature of the assessments, however, are believed to be protective of the worker. For example, conservative assumptions (e.g., maximum application rates, high daily acreages, 35-year exposure period, and first day-after-treatment residues) were used to estimate exposures and risks to workers.

Table 17
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
Mixer/Loader												
(1a) Mixing/ Loading Wettable Powder for Aerial/ Chemigation Application	cucurbits, peanuts, sugar beets	0.35	350	14	3.0e-05	3.0e-04	100	1.8e-06	1.8e-05	Not necessary	9.2e-08	9.2e-07
	pecans, strawberries, pears	0.7NC/0.6 C		7.0	5.1e-05	5.1e-04	110	3.0e-06	3.0e-05		1.6e-07	1.6e-06
	wheat, soybeans	0.7	1200	2.0	2.1e-04	2.1e-03	39	1.2e-05	1.2e-04	680	6.3e-07	6.3e-06
	apples, apricots, cherries, nectarines, plums/prunes, grapes	1	350	4.8	8.6e-05	8.6e-04	93	5.0e-06	5.0e-05	1,600	2.6e-07	2.6e-06
	almonds, beans	1.4 NC/1C		3.5	8.6e-05	8.6e-04	66	5.0e-06	5.0e-05	1,200	2.6e-07	2.6e-06
	peaches	1.6 NC/1.3C		3.0	1.1e-04	1.1e-03	58	6.5e-06	6.5e-05	1,000	3.4e-07	3.4e-06
	onions, sod farms	15 NC/11 C		0.3	9.4e-04	9.4e-03	6.2	5.5e-05	5.5e-04	110	2.9e-06	2.9e-05
	ornamentals (foliar spray) aerial	0.7 NC/0.5C	80	30.0	NA	7.8e-05	210	NA	4.6e-06	Not necessary	NA	2.4e-07
	ornamentals (foliar spray) chemigation	2.8 NC/2.1C	80	8	4.1e-05	NA	120	2.4e-06	NA		1.3e-07	NA
	ornamentals (soil directed drench) chemigation	77NC/37C	5	4.4	4.5e-05	1.4e-04	84	2.7e-06	8.5e-06	1,500	1.4e-07	4.3e-07
(1b) Mixing/ Loading Wettable Powder for Groundboom Application	cucurbits, peanuts, sugar beets	0.35	80	61	6.9e-06	6.9e-05	420	4e-07	4e-06	Not necessary	Not Necessary	2.1e-07
	strawberries	0.7 NC/0.6 C		30	1.2e-05	1.2e-04	210	6.9e-07	6.9e-06			3.6e-07
	wheat, soybeans	0.7	200	12	3.4e-05	3.4e-04	200	2.0e-06	2.0e-05		1.1e-07	1.1e-06
	grapes, potatoes	1	80	21	2.0e-05	2.0e-04	150	1.1e-06	1.1e-05		6.0e-08	6.0e-07
	beans	1.4 NC/1C		15	2.0e-05	2.0e-04	100	1.1e-06	1.1e-05		6.0e-08	6.0e-07
	onions, sod farms	15 NC/11C		1.4	2.2e-04	2.2e-03	27	1.3e-05	1.3e-04	480	6.6e-07	6.6e-06
	golf course turf	15 NC/11 C	40	2.8	1.1e-04	3.2e-04	54	6.3e-06	1.9e-05	960	3.3e-07	9.9e-07
	ornamentals (foliar spray)	2.8NC/2.1C	80	7.6	2.1e-05	6.2e-05	120	1.2e-06	3.6e-06	Not necessary	6.3e-08	1.9e-07
	ornamentals (soil drench)	77NC/37C	5	4.4	4.5e-05	1.4e-04	84	2.7e-06	8.5e-05	1,500	1.4e-07	4.3e-07

Table 17
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
(1c) Mixing/ Loading Wettable Powder for Airblast Application	pecans, pears	0.7 NC/0.6C	40	61	5.9e-06	5.9e-05	420	3.4e-07	3.4e-06	Not necessary		1.8e-07
	apples, apricots, cherries, plums/prunes, nectarines, grapes	1		42	9.8e-06	9.8e-05	290	5.7e-07	5.7e-06			3.0e-07
	almonds	1.4 NC/1C		30	9.8e-06	9.8e-05	210	5.7e-07	5.7e-06	Not necessary		3.0e-07
	peaches	1.6 NC/1.3C		26	1.3e-05	1.3e-04	200	7.5e-07	7.5e-06			3.9e-07
	ornamentals	2.8 NC/2.1C	20	30	1.0e-05	1.0e-04	210	6e-07	6e-06			3.2e-07
(1d)Mixing/ Loading Wettable Powders for Lawn Handgun Application	ornamental (foliar spray)	2.8 NC/2.1C	100	6.1	5.1e-05	5.1e-04	120	3.0e-06	3.0e-05	Not necessary	1.6e-07	1.6e-06
	ornamental (soil drench)	77NC/37C	1	22	9.1e-06	9.1e-05	150	5.3e-07	5.3e-06		2.8e-08	2.8e-07
	turf	15 NC/5.4 C	100	1.1	1.3e-04	1.3e-03	22	7.7e-06	7.7e-05	380	4.1e-07	4.1e-06
(1e) Mixing/ Loading Wettable Powder for Dip Application	bulbs	0.012 lb ai/gal	100 gallons	1,400	2.9e-07	2.9e-06	Not necessary		1.7e-07	Not necessary		
	cuttings	0.007 lb ai/gal	100 gallons	2,400	1.7e-07	5.1e-07			3e-08			
(2a) Mixing/ Loading Dry Flowable /WDG for Aerial/ Chemigation Application	cucurbits, peanuts, sugar beets	0.35	350	780	5.3e-07	5.3e-06			3.4e-06	Not necessary		9.2e-07
	pecans, strawberries	0.7 NC/0.6 C		390	9.2e-07	9.2e-06			5.9e-06			1.6e-06
	wheat, soybeans	0.7	1200	110	3.7e-06	3.7e-05	110	2.3e-06	2.3e-05	Not necessary	6.3e-07	6.3e-06
	apples, apricots, cherries, nectarines, plums/prunes	1	350	270	1.5e-06	1.5e-05	Not necessary	9.8e-07	9.8e-06		Not necessary	2.6e-06
	almonds, beans	1.4 NC/1C		190	1.5e-06	1.5e-05		9.8e-07	9.8e-06	Not necessary	2.6e-07	2.6e-06
	peaches	1.6 NC/1.3C		170	2.0e-06	2.0e-05		1.3e-06	1.3e-05		3.4e-07	3.4e-06
	onions, sod farms	15 NC/11 C		18	1.7e-05	1.7e-04	27	1.1e-05	1.1e-04	110	2.9e-06	2.9e-05
	ornamentals (foliar spray) aerial	0.7 NC/0.5 C	80	1,700	NA	1.4e-06	Not necessary	NA	8.9e-07	Not necessary	NA	Not necessary
	ornamentals (foliar spray) chemigation	2.8 NC/2.1 C	80	420	7.3e-07	NA	Not necessary		NA	Not necessary		NA
	ornamentals (soil directed drench) chemigation	37	5	510	8.1e-07	2.4e-06			1.5e-06			4.2e-07
(2b) Mixing/ Loading Dry Flowable/WDG for Groundboom Application	cucurbits, peanuts, sugar beets	0.35	80	3,400	1.2e-07	1.2e-06			7.8e-07			Not necessary
	strawberries	0.7 NC/0.6C		1,700	2.1e-07	2.1e-06			1.3e-06			3.6e-07
	wheat, soybeans	0.7	200	680	6.1e-07	6.1e-06			3.9e-06			1.1e-06

Table 17
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
	beans	1.4 NC/1 C	80	850	3.5e-07	3.5e-06			2.2e-06			6.0e-07
	onions, sod farms	15 NC/11 C		79	3.8e-06	3.8e-05	110	2.5e-06	2.5e-05	Not necessary	6.6e-07	6.6e-06
	golf course turf	15 NC/11 C	40	160	1.9e-06	5.8e-06	Not necessary	1.2e-06	3.7e-06		3.3e-07	9.9e-07
	ornamentals (foliar spray)	2.8 NC/2.1C	80	420	7.3e-07	2.2e-06	Not necessary		1.4e-06	Not necessary		3.8e-07
	ornamentals (soil drench)	37	5	510	8.1e-07	2.4e-06			1.5e-06			4.2e-07
(2c) Mixing/ Loading Dry Flowable/WDG for Airblast Application	pecans	0.7 NC/0.6C	40	3,400	1.0e-07	1.0e-06	Not necessary		6.7e-07	Not necessary		Not necessary
	apples, apricots, cherries, plums/prunes, nectarines	1		2,400	1.7e-07	1.7e-06			1.1e-06			3.0e-07
	almonds	1.4 NC/1 C		1,700	1.7e-07	1.7e-06			1.1e-06			3.0e-07
	peaches	1.6 NC/1.3C		1,500	2.3e-07	2.3e-06			1.4e-06			3.9e-07
	ornamentals	2.8 NC/2.1C	20	1,700	1.8e-07	1.8e-06			1.2e-06			3.2e-07
(2d) Mixing/ Loading Dry Flowable /WDG for Lawn Handgun Application	ornamental (foliar spray)	2.8 NC/2.1C	100	340	9.2e-07	9.2e-06	Not necessary		5.9e-06			1.6e-06
	ornamental (soil drench)	37	1	2,600	1.6e-07	1.6e-06			1.0e-06			Not necessary
	turf	15 NC/5.4C	100	63	2.4e-06	2.4e-05	96	1.6e-06	1.6e-05	380	4.2e-07	4.2e-06
(2e) Mixing/ Loading Dry Flowable/WDG for Dip Application	bulbs	0.012 lb ai/gal	100 gallons	79,000	5.2e-09	5.2e-08	Not necessary			Not necessary		Not necessary
	cuttings	0.007 lb ai/gal		140,000	3.1e-09	9.2e-09						
(3a) Mixing/ Loading Liquid Flowable Concentrates for Aerial/Chemigation Application	cucurbits, peanuts, sugar beets	0.35	350	20	2.0e-05	2.0e-04	1,600	1.4e-07	1.4e-06			6.8e-07
	pecans, strawberries, pears	0.7 NC/0.6C		9.8	3.5e-05	3.5e-04	820	2.4e-07	2.4e-06			1.2e-06
	wheat, soybeans	0.7	1200	2.9	1.4e-04	1.4e-03	240	9.7e-07	9.7e-06			4.7e-06
	apples, apricots, cherries, nectarines, plums/prunes, grapes	1	350	6.9	5.8e-05	5.8e-04	570	4.1e-07	4.1e-06	Not necessary		1.9e-06
	almonds, beans	1.4 NC/1 C		4.9	5.8e-05	5.8e-04	410	4.1e-07	4.1e-06			1.9e-06
	peaches	1.6 NC/1.3C		4.3	7.5e-05	7.5e-04	360	5.3e-07	5.3e-06			2.5e-06
	sod farms	15 NC/11 C		0.5	6.4e-04	6.4e-03	69	4.5e-06	4.5e-05	140	2.1e-06	2.1e-05
	ornamentals (foliar spray) aerial	0.7 NC/0.5C	80	43	NA	5.3e-05	3,600	NA	3.7e-07	NN	NA	NN

Table 17 Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates												
Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
	ornamentals (foliar spray) chemigation	2.8 NC/2.1C	80	11	2.8e-05	NA	890	1.9e-07	NA	Not necessary		NA
	ornamentals (soil directed drench) chemigation	37	5	13	3.1e-05	9.2e-05	1,100	2.1e-07	6.4e-07			Not necessary
(3b) Mixing/ Loading of Liquid Flowable Concentrates for Groundboom Application	cucurbits, peanuts, sugar beets	0.35	80	86	4.6e-06	4.6e-05	7,100	3.2e-08	3.2e-07			
	strawberries	0.7 NC/0.6C		43	7.9e-06	7.9e-05	3,600	5.6e-08	5.6e-07			
	wheat, soybeans	0.7	200	17	2.3e-05	2.3e-04	1,400	1.6e-07	1.6e-06			7.8e-07
	grapes	1	80	30	1.3e-05	1.3e-04	2,500	9.3e-08	9.3e-07			Not necessary
	beans	1.4 NC/1C		21	1.3e-05	1.3e-04	1,800	9.3e-08	9.3e-07			
	sod farms	15 NC/11C		2.0	1.5e-04	1.5e-03	170	1e-06	1e-05	Not necessary	4.9e-07	4.9e-06
	golf course turf	15NC/11 C	40	4.0	7.3e-05	2.2e-04	330	5.1e-07	1.5e-06	Not necessary		7.3e-07
	ornamentals (foliar spray)	2.8 NC/2.1C	80	11.0	2.8e-05	8.3e-05	890	1.9e-07	5.8e-07			Not necessary
	ornamentals (soil drench)	77NC/37C	5	6.2	3.1e-05	9.2e-05	520	2.1e-07	6.4e-07			3.1E-07
(3c) Mixing/ Loading of Liquid Flowable Concentrates for Airblast Application	pecans, pears	0.7 NC/0.6C	40	86	4.0e-06	4.0e-05	7,100	2.8e-08	2.8e-07	Not necessary		
	apples, apricots, cherries, plums/prunes, nectarines, grapes	1		60	6.6e-06	6.6e-05	5,000	4.6e-08	4.6e-07			
	almonds	1.4 NC/1 C		43	6.6e-06	6.6e-05	3,600	4.6e-08	4.6e-07			
	peaches	1.6 NC/1.3C		38	8.6e-06	8.6e-05	3,300	6e-08	6e-07			
	ornamentals	2.8 NC/2.1C	20	43	6.9e-06	6.9e-05	3,600	4.9e-08	4.9e-07			
(3d) Mixing/ Loading Liquid Flowable Concentrates for Lawn Handgun Application	ornamental (foliar spray)	2.8NC/2.1 C	100	8.6	3.5e-05	3.5e-04	710	2.4e-07	2.4e-06	Not necessary		1.2e-06
	ornamental (soil drench)	77NC/37C	1	31	6.1e-06	6.1e-05	2,600	4.3e-08	4.3e-07			Not necessary
	turf	15NC/5.4C	100	1.6	8.9e-05	8.9e-04	130	6.3e-07	6.3e-06	Not necessary		3e-06
(3e) Mixing/ Loading Liquid Flowable Concentrates for Dip Application	bulbs	0.012 lb ai/gal	100 gallons	2,000	2.0e-07	2.0e-06	Not necessary		1.4e-08	Not necessary		
	cuttings	0.007 lb ai/gal		3,400	1.2e-07	3.5e-07	Not necessary					

Table 17
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
(4a) Loading Granular Formulations for Aerial Application	ornamentals	27	80	130	NA	3.2e-05	140	NA	8.1e-06	Not necessary	NA	6.4e-07
(4b) Loading Granular Formulation For Mechanical Ground Application	ornamentals	27	80	130	4.0e-06	4.0e-05	Not necessary	1e-06	1e-05	Not necessary	8.0e-08	8.0e-07
	turf	11	40	630	8.2e-07	2.4e-06	Not necessary		6.2e-07	Not necessary		
		5.4		1,300	4.0e-07	1.2e-06			3e-07			
	sod farms	11	80	310	1.6e-06	1.6e-05	Not necessary	4.1e-07	4.1e-06	Not necessary	3.3e-08	3.3e-07
		5.4		640	8.0e-07	8.0e-06	Not necessary		2.0e-06	Not necessary		1.6e-07
(5) Loading Dusts (Fenske et al., 1991(k) and Stevens and Davis, 1980 (l)	peanut seeds (gloves)	0.047	20 (l)	See PPE			7,600	6.5e-08	2.2e-07	No Data		
	potato seed pieces (gloves)	1.2 (l)	30 (l)				200	2.5e-06	8.3e-06			
Applicator												
(6) Applying Sprays Aerially	cucurbits, peanuts, sugar beets	0.35	350	See Eng. Controls						10,000	Not applicable	4.1e-07
	pecans, strawberries, pears	0.7NC/0.6C								5,000		7.1e-07
	wheat, soybeans	0.7	1200							1,500		2.8e-06
	apples, apricots, cherries, nectarines, plums/ prunes, grapes	1	350							3,500		1.2e-06
	almonds, beans	1.4NC/1 C								2,500		1.2e-06
	peaches	1.6NC/1.3C								2,200		1.5e-06
	onions, sod farms	15NC/11C								230		1.3e-05
	ornamentals (foliar spray) aerial	0.7NC/0.5C	80							22,000		1.1e-07
(7) Applying Granulars Aerially	ornamentals	27	80							250	NA	2.5E-5
(8) Applying with Groundboom	cucurbits, peanuts, sugar beets	0.35	80	12,000	3.9e-08	3.9e-07	Not necessary					
	strawberries	0.7NC/0.6C		5,800	6.7e-08	6.7e-07						
	wheat, soybeans	0.7	200	2,300	2.0e-07	2.0e-06	Not necessary		1.0e-06	Not necessary		4.5e-07
	grapes, potatoes	1	80	4,100	1.1e-07	1.1e-06			6.0e-07			Not necessary
	beans	1.4NC/1C		2,900	1.1e-07	1.1e-06			6.0e-07			

Table 17
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
	onions, sod farms	15NC/11C		270	1.2e-06	1.2e-05	Not necessary	6.6e-07	6.6e-06			2.8e-06
	golf course turf	15NC/11C	40	550	6.1e-07	6.1e-06	Not necessary		3.3e-06			1.4e-06
	ornamentals (foliar spray)	2.8NC/2.1C	80	1,500	2.3e-07	7.0e-07			Not necessary			Not necessary
	ornamentals (soil drench)	77	5	850	5.4e-07	1.6e-06			8.6e-07			
		37		1,800	2.6e-07	7.7e-07	Not necessary					
(9) Applying with an Airblast Sprayer	pecans, pears	0.7NC/0.6C	40	620	5.8e-07	5.8e-06	Not necessary		3.2e-06	Not necessary		3.5e-07
	apples, apricots, cherries,plums/prunes, nectarines, grapes	1		430	9.6e-07	9.6e-06			5.3e-06			5.8e-07
	almonds	1.4NC/1C		310	9.6e-07	9.6e-06	Not necessary		5.3e-06	Not necessary		5.8e-07
	peaches	1.6NC/1.3C		270	1.3e-06	1.3e-05	Not necessary	7.0e-07	6.9e-06	Not necessary	7.5e-08	7.5e-07
	ornamentals	2.8NC/2.1C	20	310	1.0e-06	1.0e-05	Not necessary		5.5e-06	Not necessary		6.1e-07
(10) Applying with a Handgun Sprayer	ornamentals (foliar spray)	2.8NC/2.1C	5	530	5.6e-07	5.6e-06			2.1e-06	Not feasible		
	ornamentals (soil drench)	77	0.05	2,000	2.1e-07	2.1e-06			7.7e-07			
		37		4,000	9.9e-08	9.9e-07			3.7e-07			
	turf	15NC/5.4C	5	99	1.5e-06	1.5e-05	140	5.4e-07	5.4e-06			
(11) Applying Granular Formulations with a Tractor-Drawn Spreader	ornamentals	27	40	300	1.7e-06	1.7e-05	Not necessary	4.7e-07	4.7e-06	Not necessary	3.2e-07	3.2e-06
	turf	11		730	6.7e-07	6.7e-06	Not necessary		1.9e-06	Not necessary		1.3e-06
		5.4		1,500	3.3e-07	3.3e-06			9.3e-07			Not necessary
(12) Applying Dip Treatment	bulbs	0.012 lb ai/gal	100 gallons	No Data								
	cuttings	0.007 lb ai/gal										
(13) Applying Dust as a Potato Seed Treatment (Stevens and Davis, 1981)	cutting/sorting (gloves)	1.2 (l)	30 (l)	No Data - See PPE			2,700	1.6e-07	5.4e-07	Not feasible/not necessary		
	planter/operator (enclosed cab)			See Eng. Controls						3,600	1.3e-07	4.5e-07
	planter/observer (no gloves)			4,400	1.1e-07	3.6e-07	Not necessary			No Data/Not necessary		
Mixer/Loader/Applicator												

Table 17
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
(14) Mixing/ Loading/Applying Liquids using High Pressure Handwand	ornamentals (foliar spray)	0.007 lb ai/gal	1000 gallons	See PPE			270	7.7e-07	2.3e-06	Not feasible		
(15) Mixing/ Loading/Applying WP using Low Pressure Handwand	ornamentals (soil drench and foliar spray)	0.007 lb ai/gal	40 gallons	See PPE			1,300	2.5e-07	1.5e-06			
	turf (j)	15NC/5.4C	0.5				110	2.4e-06	1.4e-05			
(16) Mixing/ Loading/Applying Liquid Formulations using Low Pressure Handwand	ornamentals (soil drench and foliar spray)	0.007 lb ai/gal	40 gallons	250	2.7e-06	1.6e-05	Not necessary	1.2e-08	7.2e-08			
	turf (j)	15NC/5.4C	0.5	9.3	2.6e-05	1.5e-04	1,300	1.2e-07	7e-07			
(17) Mixing/ Loading/Applying Dry Flowables using Low Pressure Handwand	ornamentals (soil drench and foliar spray)	0.007 lb ai/gal	40 gallons	No Data						Not feasible		
	turf (j)	15NC/11C	0.5									
(18) Mixing/ Loading/Applying with a Backpack Sprayer	ornamentals (soil drench and foliar spray)	0.007 lb ai/gal	40 gallons	See PPE			8,900	5.1e-08	3.1e-07	Not feasible		
	turf(j)	15NC/5.4C	0.5				330	5e-07	3e-06			
(19a) Mixing/ Loading/Applying Liquid Formulations with a Handgun Sprayer (ORETF data, MRID 44972201)	ornamental (foliar spray)	2.8NC/2.1C	5	710	4.3e-07	4.3e-06	Not necessary		1.5e-06	Not feasible		
	ornamental (soil drench)	77NC/37C	0.05	2,600	7.5e-08	7.5e-07			2.7e-07			
	turf	15NC/5.4C	5	130	1.1e-06	1.1e-05	Not necessary	3.9e-07	3.9e-06			
(19b) Mixing/ Loading/ Applying Dry Flowables (WDG) with a Handgun Sprayer (ORETF data, MRID 44972201)	ornamental (foliar spray)	2.8NC/2.1C	5	480	5.1e-07	5.1e-06	Not necessary		1.7e-06	Not feasible		
	ornamental (soil drench)	37NC/37C	0.05	3,600	8.9e-08	8.9e-07			3e-07			
	turf	15NC/5.4C	5	90	1.3e-06	1.3e-05	120	4.4e-07	4.4e-06			

Table 17
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
(19c) Mixing/ Loading/ Applying Wettable Powders with a Handgun Sprayer (ORETF data, MRID 44972201)	ornamental (foliar spray)	2.8NC/2.1C	5	310	1.1e-06	1.1e-05	Not necessary	3.3e-07	3.3e-06	Not feasible		
	ornamental (soil drench)	77NC/37C	0.05	1,100	2.0e-07	2.0e-06	Not necessary		5.8e-07			
	turf	15NC/5.4C	5	58	2.9e-06	2.9e-05	110	8.5e-07	8.5e-06			
(20) Loading/ Applying Granules to Turf using Belly Grinder	ornamentals	27	1	24	1.7e-05	1.7e-04	45	9.0e-06	9.0e-05	Not feasible		
	turf	11		60	6.8e-06	6.8e-05	100	3.7e-06	3.7e-05			
		5.4		120	3.3e-06	3.3e-05	Not necessary	1.8e-06	1.8e-05			
(21) Loading/ Applying Granules to Turf using Push-Type Spreader (ORETF data, MRID 44972201)	ornamentals	27	5	120	3.5e-06	3.5e-05	180	1.1e-06	1.1e-05	Not Feasible		
	turf	11		300	1.4e-06	1.4e-05	Not necessary	4.4e-07	4.4e-06			
		5.4		610	7.0e-07	7.0e-06	Not necessary		2.2e-06			
(22) Loading/ Applying Dust as a Seed Treatment (dry) in Planter Box (k)(Fenske et al., 1990)	peanuts	0.047	20	No Data			710	5.6e-07	5.6e-06	No Data		
(23) Mixing/ Loading/Applying a Dip Treatment	bulbs	0.012 lb ai/gal	100 gallons	No Data								
	cuttings	0.007 lb ai/gal										
Flagger												
(24) Flagging Aerial Spray Applications	cucurbits, peanuts, sugar beets	0.35	350	3,900	1.1e-07	1.1e-06	Not necessary		7.6e-07	Not necessary		3.9e-07
	pecans, pears, strawberries,	0.7NC/0.6C	350	2,000	1.9e-07	1.9e-06			1.3e-06			6.7e-07
	wheat, soybeans	0.7	350	2,000	2.2e-07	2.2e-06			1.5e-06			7.8e-07
	apples, apricots, cherries, nectarines, plums/prunes, grapes	1	350	1,400	3.2e-07	3.2e-06			2.2e-06			1.1e-06
	almonds, beans	1.4NC/1C		990	3.2e-07	3.2e-06			2.2e-06			1.1e-06

Table 17
Thiophanate-methyl: Summary of Occupational Handler Short- and Intermediate-Term Exposure and Cancer Risk Estimates

Exposure Scenario	Crop Type/Use	Maximum Application Rate (lb ai/acre or lb ai/gallon) (a)	Amount Treated Per Day (Acres or Gallons) (b)	Baseline Risks (c)			PPE Mitigation Risks (d)			Engineering Control Risks (e)		
				Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk(i)		Combined Dermal and Inhalation MOE (f)	Cancer Risk (i)	
					Private (g)	Commercial (h)		Private (g)	Commercial (h)		Private (g)	Commercial (h)
	peaches	1.6NC/1.3C		860	4.1e-07	4.1e-06			2.8e-06			1.4e-06
	onions, sod farms	15NC/11C		92	3.5e-06	3.5e-05	120	2.4e-06	2.4e-05	250	1.2e-06	1.2e-05
	ornamentals (foliar spray)	2.8NC/2.1C	80	2,200	1.5e-07	1.2e-06	Not necessary		8.4e–07	Not necessary		Not necessary
(25) Flagging Aerial Granular Applications	ornamentals	27	80	750	6.1e-07	4.8e-06			2e-06			5.1e-06

NA=Not applicable; NC= non-cancer; C= cancer, NN=not necessary

(a) Application rates are the maximum application rates determined from EPA registered labels. Typical application rate (used in the cancer risk estimates) were determined from EPA registered labels when a range of application rates was specified. Maximum application rate was used as a surrogate for typical rate when a range was not specified.
NC= non-cancer; C= cancer

(b) Amount handled per day values are based on HED Exposure SAC Policy # 009 "Standard Values for Daily Acres Treated in Agriculture," revised June 23, 2000, or best professional judgment when data is not available. Ornamental acres treated aerially is based on person communication with ANLA on 12/7/00.

(c) Baseline clothing assumes long pants, long sleeved shirt, no gloves, open mixing/loading, open cab/tractor for applications, and no respirator or dust mask.

(d) PPE assumes gloves and no respirator for most cases, and in some cases assumes double layer clothing. See Occupational/Residential Chapter for inputs and calculations.

(e) Engineering Controls include: Water-Soluble Packets or Enclosed Cab Aircraft

(f) Short/Intermediate-term dermal MOE = NOAEL (100 mg/kg/day / daily dermal dose (mg/kg/day). Short/Intermediate-term inhalation MOE = NOAEL (10 mg/kg/day / daily inhalation dose (mg/-kg/day). Where daily dermal dose = dermal/inhalation unit exposure (mg/lb ai) x application rate (lb ai/acre or gallons/day) x amount handled per day (acres or gallons/day) / body weight (60 kg female >13 yrs). Short/Intermediate-term total MOE = 1 / 1/dermal MOE) + (1/inhalation MOE).

(g) Majority of private applicator treatments per year is 3, which is based on labeled number of treatments to an individual site (e.g., farm, nursery, golf course) and represents number of days per year of expected exposure. BEAD and other use data were used in determining treatment day estimates (e.g., facility or farm size / acres per day in footnote b = exposure days / year).

(h) Most commercial applicator treatments per year is 30, which is based on treatment of multiple sites or farms and represents number of days per year of expected exposure.

(i) Cancer Risk = Total LADD (mg/kg/day) x Q_1*. Where Q_1* is 0.0138 mg/kg/day^{-1}; where total LADD (mg/kg/day) = ADD (mg/kg/day) x treatment days per year (for private or commercial as appropriate) / 365 days/year x 35 years worked / 70 year lifetime; and where ADD (mg/kg/day) = absorbed daily dermal dose (mg/kg/day) + daily inhalation dose (mg/kg/day) where absorbed daily dermal dose = dermal unit exposure (mg/lb ai) x typical application rate (lb ai/acre or gallons/day) x amount handled per day (acres or gallons/day) x dermal absorption factor (7%) / body weight (70 kg adult), and inhalation dose = inhalation unit exposure (mg/lb ai) x application rate (lb ai/acre or gallons/day) x amount handled per day (acres or gallons/day) / body weight (70 kg).

(j) For turf applications 3336WP label: 2 gals min/1000 sq ft x 40 gal/day estimated rate = 20,000 sq ft or 0.5 acre/day.

(k) Unit exposure values based on a lindane study of peanut treated seed, Fenske et al., 1990.

(l) Exposure data for dust applications based on an exposure study by Stevens and Davis, 1981 (i.e., Captan treated potato seed piece and potato planting study) . The dermal exposure was adjusted to the use of thiophanate-methyl 2.5% dust at 0.025 lb/100 lb seed potatoes (TOPS 2.5D Reg No. 7501-32). It was estimated that 30 acres could be treated in an 8 hour day, based on tractor speed, capacity, and lbs seed/acre. Cancer risk was based on 3-10 planting days per year , assuming USDA estimates of farm size (i.e., 100-300 acres depending on geographic region). Exposure values from the study (mg/hr) were ÷ 4.5 lb ai/hr , in order to determine a standard unit exposure values (mg/lb ai), assuming 30 acres treated /day x 1.2 lb ai/acre ÷ 8 hrs worked/day.

Table 18 Thiophanate-methyl: Summary of Postapplication Occupational Short-, Intermediate and Long-Term Non-Cancer and Cancer Risks by Crop and Activity						
Crop Treated (Potential for Dermal Contact)	**Transfer Coefficient (cm^2/hr) (a)**	**Activities**	**REIs MOE>100 (DAT)**	**MOE at DAT 1**	**Exposure Duration (Days/Year)**	**Cancer Risk Estimate Avg DAT 1-14**
Risk Estimates Using Apple DFR Study Data EPA MRID 44876301						
Apples; Cherries, nectarines, apricots, plums/prunes	8000	Thinning	NY: 6 WA: 28	NY: 42 WA: 48		
	3000	Hand pruning, propping, hand harvesting	NY: 1 WA: 0	NY: 110 WA: 130	apple: 60	2.6e-05 to 5.7e-05
					cherries: 45	2e-05 to 4.3e-05
Peaches	8000	Thinning	NY: 8 WA: 56	NY: 28 WA: 32		
	3000	Hand pruning, propping, hand harvesting	NY: 3 WA: 14	NY: 74 WA: 84	45	2.7e-05 to 5.6e-05
Almonds	2500	Hand harvesting, hand pruning	NY: 1 WA: 0	NY: 100 WA: 120	60	2.3e-05 to 4.8e-05
Pecans	2500	Hand harvesting, hand pruning	NY: 0 WA: 0	NY: 170 WA: 230	60	1.4e-05 to 2.9e-05
Pears	8000	Thinning	NY: 4 WA: 14	NY: 63 WA: 72		
	3000	Harvesting, pruning, training, tying	NY: 0 WA: 0	NY: 140 WA: 190	60	1.6e-05 to 3.4e-05
Grapes	10,000	Grape girdling and cane turning	NY: 7 WA: 28	NY: 34 WA: 39		
	5000	Hand harvesting, leaf pulling, thinning, pruning, training/tying	NY: 4 WA: 14	NY: 67 WA: 77	105	7.9e-05 to 1.7e-04
Woody Ornamentals	8000	Hand harvesting, pruning, pinching, and transplanting	NY: 11 WA: >84	NY: 16 WA: 18	30	1.1e-04 to 1.6e-04

Table 18 Thiophanate-methyl: Summary of Postapplication Occupational Short-, Intermediate and Long-Term Non-Cancer and Cancer Risks by Crop and Activity						
Crop Treated (Potential for Dermal Contact)	**Transfer Coefficient (cm^2/hr) (a)**	**Activities**	**REIs MOE>100 (DAT)**	**MOE at DAT 1**	**Exposure Duration (Days/Year)**	**Cancer Risk Estimate Avg DAT 1-14**
Risk Estimates Using Cut Flower DFR Study: Average of Rose & Mum Data EPA MRID 45027501.						
Cut Flowers	4500 [Brouwer, et al.]	Typical greenhouse activities such as pruning, thinning, harvesting, scouting, irrigating	48	18	90	4.3e-04
Herbaceous Ornamentals	7000	Hand harvesting, pruning, pinching, thinning	59	11		
	4000	Irrigating, scouting	45	19	90	3.8e-04
	2500	Hand weeding	33	30		
Risk Estimates Using Strawberry DFR Study Data EPA MRID 44866201						
Strawberries	1500	Hand harvest, pinch, prune, train	0	240	180	1.1e-05
	400	Irrigate, scout, weed	0	910		
Wheat	1500	Irrigate, scout	0	240	15	1.1e-06
Cucurbits	2500	hand harvest, prune, leaf pulling	0	290	60	3.6e-06
	1500	Hand weed, scout, irrigate	0	490		
Sugar beets	1500	Irrigate, scout	0	490	30	1.1e-06
Soybeans	1500	Irrigate, scout	0	240	45	3.2e-06
Beans	2500	Hand harvest	1	110	45	7.7e-06
	1500	Irrigate, scout	0	120		
Potatoes	2500	Hand harvest	0	100	45	7.7e-06

Table 18 Thiophanate-methyl: Summary of Postapplication Occupational Short-, Intermediate and Long-Term Non-Cancer and Cancer Risks by Crop and Activity						
Crop Treated (Potential for Dermal Contact)	**Transfer Coefficient (cm^2/hr) (a)**	**Activities**	**REIs MOE>100 (DAT)**	**MOE at DAT 1**	**Exposure Duration (Days/Year)**	**Cancer Risk Estimate Avg DAT 1-14**
Potatoes	1500	Irrigate, scout mature plants	0	170		
Herbaceous Ornamentals	7000	Hand harvest, prune, thin, transplant	3	13	120	1.2e-04
	1500	Scout, irrigate	1	260		
Risk Estimates Using Turf TTR Study Data EPA MRID 45000701						
Turf: Sod farm	16,500	Hand harvest, transplant, weed	Irrig: 2 Dry: 7	Irrig: 66 Dry: 46	90	1.3e-05 to 3.9e-05
	500	Seed, scout, mech. weed, aerate, fertilize, irrigate, mow	0	1400/ 1300		
Turf: Golf course	16,500	Transplant, hand weed	Irrig: 2 Dry: 7	Irrig: 66 Dry: 46		
	500	Seed, scout, mech. weed, aerate, fertilize, irrigate, mow	0	1400/ 1300	90	3.8e-07 to 1.2e-06

(a) Standard HED values for transfer coefficients based on best available data, including ARTF studies and Thiophanate-methyl study by Brouwer, et al., for greenhouse flowers.

8.0 INCIDENTS

A review of incident data sources found that relatively few incidents were reported for thiophanate-methyl. A detailed summary of these incidents is provided in the attached memorandum from J. Blondell and M. Spann to J. Evans, August 15, 1997. The majority of significant symptoms were respiratory or eye irritation, particularly when handling dry formulations. Eleven of 37 California incident reports were judged related to thiophanate-methyl alone, and the majority of the five systemic illnesses occurred due to a crew of workers sprinkling thiophanate-methyl from coffee cans onto potato seed pieces. Symptoms included shortness of breath, chest pains, burning eyes, dizziness, and fatigue. The Incident Data System cited 2 incidents in 1994, both of which were reportedly a result of spray drift. One case reported respiratory irritation, the other eye irritation, with no follow up information. Thiophanate-methyl was not included on the list of the top 200 chemicals for which the National Pesticide Telecommunications Network (NPTN) received calls from 1984-1991. Poison Control Center data for 1993 through 1998 listed 76 exposures to thiophanate methyl. The overwhelming majority of these cases had only exposure or minor symptoms. There were no life-threatening cases or deaths as a result of exposure to oxadiazon. There were 9 cases that had moderate effects. Among these, dermal effects were the most common. The number of cases reported in occupational and non-occupational categories and among children and adults was too few to warrant a more extensive analysis. However, based on this limited information and other reports, oxadiazon is capable of mild toxic and irritant effects.

9.0 DEFICIENCIES / DATA NEEDS (CONFIRMATORY DATA)

Additional data requirements have been identified in the attached Science Chapters and are summarized here.

Toxicology Data for OPPTS Guideline:

At this time, the toxicology database for thiophanate-methyl is incomplete. The Hazard Identification Assessment Review Committee (HIARC, meeting of April 8, 1999, and September 26, 2000) requested that rat acute and subchronic neurotoxicity screening studies be submitted and that a developmental neurotoxicity study be placed in 'reserve' status pending the results of these studies and a developmental neurotoxicity study with MBC. The HIARC also requested a 90 day rat inhalation study because an unacceptable 14-day inhalation study showed possible respiratory effects from thiophanate-methyl exposure at lower concentrations than those associated with developmental effects and because occupational exposures are potentially long-term in green houses. The Cancer Assessment Review Committee (CARC, April 28, 1999 meeting) requested submission of the following additional genotoxicity studies: a preincubation *Salmonella typhimurium* mammalian microsome gene mutation assay, a mouse lymphoma L5178 cell forward gene mutation assay with colony sizing and a mouse *in vivo* bone marrow assay with antikinetochore staining. In addition, the metabolite 2-aminobenzimidazole metabolite should be tested at minimum in the *S. typhimurium* mammalian microsome gene mutation assay.

Toxicology data for carbendazim (Methyl 2-Benzimidazole Carbamate) or MBC, the primary environmental breakdown product of thiophanate-methyl and benomyl, are also considered in this assessment, and are incomplete. The HIARC requested two toxicity studies with MBC, a 21 day dermal toxicity study in rats and a developmental neurotoxicity study in rats. In addition, the 2-generation rat reproduction and subchronic studies for MBC fail to meet the Subdivision F Guidelines.

Product and Residue Chemistry Data for OPPTS Guidelines

The following confirmatory data requirements remain outstanding as discussed in the Revised Product and Residue Chemistry Chapter (J. Morales, March 15, 2001; D272013) or are now required:

Product Chemistry:

830.1620 - Starting Materials and Manufacturing Process
830.1670 - Discussion of Formation of Impurities
830.6313 - Stability
830.7050 - UV/Visible Absorption

Residue Chemistry:

860.1200 - Directions for Use
860.1340 - Residue Analytical Methods
860.1360 - Multiresidue Method Testing

860.1380 - Storage Stability Data
860.1500 - Magnitude of the Residue in Plants
860.1520 - Magnitude of the Residue in Processed Food/Feed
860.1900 - Field Accumulation in Rotational Crops

Occupational Exposure Data for OPPTS Guidelines

There are insufficient information and data to adequately assess seed and dip applications. HED requests data to support these registered uses.

10.0 REFERENCES

Nakai, M.,. Hess, R.A., Moore, B.J., Guttroff, R.F., Strader, L.F., and, Linder, R.E. 1992. "Acute and Long-term Effects of a Single Dose of the Fungicide Carbendazim (Methyl 2-Benzimidazole Carbamate) on the Male Reproductive System in the Rat." Journal of Andrology. 13(6):507-517.

Outdoor Residential Pesticide use and Usage Survey and National Gardening Association Survey. 1999. Submitted by the Outdoor Residential Exposure Task Force. D. Johnson, Steward Agricultural Research Services, Inc. R. Thomson, DOANE Marketing Research, Inc. B. Butterfield, National Gardening Association. November 12. Volume 8 and 9 of 17.

US Environmental Protection Agency, 1999. Guidance for Conducting Health Risk Assessment of Chemical Mixtures - External Scientific Peer Review Draft, NCEA-C-0148, April 1999, http://www.epa.gov/ncea/mixtures.htm

Wood et al. 1982. Chronic feeding study in CD-1 mice (2 yrs). MRID # 256028, and 256029

APPENDIX A
SUMMARY OF TOXICOLOGICAL DATA
FOR THIOPHANATE-METHYL AND MBC

Table A-1: toxicity studies for thiophanate-methyl		
GUIDELINE/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day)**
870.3100 [82-1(a)] 90-Day Dietary Toxicity Study in Rats	MRID No. 42001701 Date: 1990 Acceptable-guideline% 0, 13.9, 155.0, 293.2, 426.9 or 564.7 & 0, 15.7, 173.4, 323.0, 478.8 or 647.3 Tech., 96.55% a.i.	NOAEL = 15.7 mg/kg/day LOAEL = 155.0 mg/kg/day, based on anemia, increased serum cholesterol and calcium (males), increased liver and thyroid weights, increased kidney (males) weight and increased incidence of thyroid hyperplasia/hypertrophy, liver swelling and lipofuscin deposition, and glomerulonephrosis (males) were observed. At higher dose levels, effects included increased serum cholinesterase (males), increased thymus weight (females), increased incidence of glomerulonephritis (females) and fatty degeneration of the adrenal cortex were also reported.
870.3150 [82-1(b)] 90-Day Oral (Capsule) Toxicity Study in Beagle Dogs	MRID No. 42311801 Date: 1992 Acceptable-guideline 0, 50, 200 or 800 in gelatin capsules (HDT lowered to 400 on day 50 due to excessive toxicity) Tech., 96.55% a.i.	NOAEL = 50 mg/kg/day LOAEL = 200 mg/kg/day, based on thin/dehydrated appearance, tarry stools, decreased body weight/weight gain, decreased food consumption, slight anemia, increased serum cholesterol, decreased serum T3/T4 (females), increased liver and thyroid weights, thyroid follicular cell hypertrophy and hyperplasia, hypoplasia/atrophy of the prostate, thymic involution/atrophy (males) and depletion of spleen lymphoid cells. At 800/400 mg/kg/day, mortality (1 male), increased platelet count were also observed.
870.3200 [82-2] 21-Day Dermal Toxicity Study in New Zealand White Rabbits	MRID No. 42110801 Date: 1991 Acceptable-guideline 0, 100, 300 or 1000, moistened with water (5 days/week, 6 hrs/day) Tech., 96.55% a.i.	Systemic toxicity NOAEL = 100 mg/kg/day Systemic toxicity LOAEL = 300 mg/kg/day, based on decreased food consumption in females. At 1000 mg/kg/day, consumption also decreased in males. Slight dermal irritation was observed at all dose levels.
870.3465 [82-4] 14-Day Inhalation Toxicity Study in HSD:(SD) Rats	MRID No. 42527601 Date: 1992 Unacceptable-nonguideline0.0, 0.00514, 0.0151 or 0.247 mg/L Tech., 5.2% a.i. (Tops® 5 formulation)	NOAEL = 0.00514 mg/L LOAEL = 0.0151 mg/L, based on increased incidence of alveolar macrophages, pneumonocyte hyperplasia of the lung and nonsuppurative alveolitis. At 0.247 mg/L, decreased body weight gain (females) and increased incidence of lung microgranulomas (both sexes) were also observed.

Table A-1: toxicity studies for thiophanate-methyl		
GUIDELINE/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day)**
870.4100 [83-1b] 1-Year Oral (Capsule) Study in Beagle Dogs	MRID No. 42311801 Date: 1992 Acceptable-guideline 0, 8, 40 or 200 in gelatin capsules Tech., 96.55% a.i.	NOAEL = 8 mg/kg/day LOAEL = 40 mg/kg/day, based on decreased body weight/weight gain, markedly increased serum TSH (1 male) and decreased T4 (males), increased serum cholesterol (males), increased abs/rel thyroid weights (both sexes) and thyroid follicular cell hypertrophy (females). At 200 mg/kg/day, tremors in all dogs 2-4 hrs postdosing (most on day 1; sporadically through day 17), slight anemia, increased serum alkaline phosphatase and cholesterol, increased relative liver weight, thyroid follicular cell hypertrophy in males and hyperplasia (both sexes) were also observed.
870.4200b [83-2b] 18-Month Dietary Carcinogenicity Study in CD-1 Mice	MRID No. 42607701 Date: 1992 Acceptable-guideline % 0, 23.7, 98.6, 467.6 or 1078.8 mg/kg/day; & 0, 28.7, 123.3, 557.9 or 1329.4 mg/kg/day Tech., 95.93% and 96.55% a.i.	Systemic toxicity NOAEL = 23.7 mg/kg/day Systemic toxicity LOAEL = 123.3 mg/kg/day, based on hepatocellular hypertrophy in females. At $98.6 mg/kg/day, decreased body weights,, sporadic effects on circulating T4 and TSH, increased thyroid and liver weights, increased heart weight (females), increased hepatocellular hypertrophy and increased atrial thrombosis were also observed. At the HDT, mortality was increased in both sexes. Increased incidence of hepatocellular adenomas in males at $467.6 mg/kg/day (control to high dose, 9%, 17%, 15%, 42% and 57%) and in females at $123.3 mg/kg/day (0%, 0%, 8%, 24% and 56%). Both sexes showed significant increasing trends and pair wise increases at the highest two dose levels.

Table A-1: toxicity studies for thiophanate-methyl		
GUIDELINE/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day)**
870.4300 [83-5] 24-Month Dietary Chronic Toxicity/ Carcinogenicity Study in F-344 Rats	MRID No. 42896601 Date: 1993 Acceptable-guideline % 0, 3.3, 8.8, 54.4 or 280.6 & 0, 3.8, 10.2, 63.5 or 334.7 Tech., 96.55% a.i.	NOAEL = 8.8 mg/kg/day LOAEL = 54.4 mg/kg/day, based on decreased body weight/weight gain (males; marginal in females), decreased food efficiency (males; marginal in females), sporadic effects on circulating T3/T4 and TSH, increased serum cholesterol and creatinine, decreased serum cholinesterase in females, increased liver, thyroid and kidney weights, liver hypertrophy and lipofuscin accumulation, thyroid hypertrophy and hyperplasia and lipofuscin accumulation in the kidney. At$280.6 mg/kg/day, excessive mortality in males (2/50 survivors at termination), decreased body weight/weight gain in females, mild anemia, increased urinary protein, hyperparathyroidism (primarily in males), systemic calcification, increased severity of nephropathy and increased severity of liver and thyroid effects were also observed. The HDT was considered excessive in males. Increased incidence of thyroid follicular cell adenoma in males (control to high dose, 2%, 0%, 0%, 6% and 27%) and females (0%, 0%, 0%, 2% and 4%). Significantly increased trend in both sexes; pair wise incidence in males at high dose. Follicular cell carcinomas also observed in high dose males at high dose (11% vs. 0% all other doses; significant trend and pair wise comparison). Combined incidence significantly increased at high dose (2%, 0%, 0%, 6% and 32%) with positive increasing trend.
870.3700a [83-3(a)] Developmental toxicity study in Crl: COBS CD rats (gavage)	MRID No. 00106090 Date: 1981 Unacceptable-guideline (upgradable with submission of dosing solution analyses, maternal clinical sign and food consumption data, and individual litter data) 0, 100, 300 or 1000 (gavage in 5% aq. gum arabic) tech., 97.2% a.i.	Maternal NOAEL = 300 mg/kg/day* Maternal LOAEL = 1000 mg/kg/day*, based on decreased body weight gain. Developmental NOAEL $1000 mg/kg/day* Developmental LOAEL >1000 mg/kg/day* * All endpoints tentative pending submission of additional information to upgrade study
870..3700a [83-3(a)] Developmental toxicity study in Crl: COBS CD rats (diet)	MRID No. 00146643 Date: 1985 Acceptable-nonguideline 0, 18, 85, or 163 (0, 250, 1200 or 2500 ppm in diet) tech., 95.3% a.i.	Maternal NOAEL = 18 mg/kg/day Maternal LOAEL = 85 mg/kg/day, based on decreased food consumption. Developmental NOAEL $163 mg/kg/day (HDT) Developmental LOAEL none established

Table A-1: toxicity studies for thiophanate-methyl		
GUIDELINE/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day)**
870.3700b [83-3(b)] Developmental Toxicity Study in New Zealand White Rabbits	MRID No. 40028801 Date: 1986 Acceptable-guideline 0, 2, 6 or 20 (gavage in 1% aq. methyl cellulose) tech., 96.2% a.i.	Maternal NOAEL = 6 mg/kg/day Maternal LOAEL = 20 mg/kg/day, based on transiently decreased body weight gain, increased abortion/total litter loss Developmental NOAEL = 2 mg/kg/day Developmental LOAEL = 6 mg/kg/day, based on increased fetal/litter incidence of asymmetric pelvis and possibly thickened ribs at costal cartilage
870.3800 [83-4] Two-Generation Reproductive toxicity Study in Crl:CD(SD)BR Rats	MRID Nos. 42899101 to -05; 43624401 Date: 1993 (addendum 1995) Acceptable-guideline % 0, 13.7, 43.3 or 138.9; & 0, 15.5, 54.0 or 172.0 (in diet) tech., 95.9% a.i.	Parental systemic NOAEL <13.7 mg/kg/day Parental systemic LOAEL = 13.7 mg/kg/day, based on hepatocellular hypertrophy and thyroid hypertrophy/hyperplasia. At $43.3 mg/kg/day, slightly decreased body weight gains in males and at 138.9 mg/kg/day, increased liver and thyroid weights (both sexes). Reproductive NOAEL $ 138.9 mg/kg/day (HDT) Reproductive LOAEL > 138.9 mg/kg/day Offspring NOAEL = 13.7 mg/kg/day Offspring LOAEL = 43.3 mg/kg/day, based on slightly reduced body weights of the F2b offspring during lactation.
870.3800 [83-4] Three-Generation Reproductive Toxicity Study in CD Rats	MRID No. 00117870 Date: 1972 Unacceptable-guideline (upgradable with submission of test material purity) 0, 2, 8 or 32 (estimated from ppm in diet) purity a.i. not stated	Parental systemic/reproductive NOAEL $32 mg/kg/day Parental systemic/reproductive LOAEL >32 mg/kg/day Offspring NOAEL = 8 mg/kg/day Offspring LOAEL = 32 mg/kg/day, based on slightly decreased mean litter weights.

NOAEL = No Observable Adverse Effect Level
LOAEL = Lowest Observable Adverse Effect Level
NA = Not applicable

Table A-2. Toxicity Studies for MBC		
GDLN/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day) (1)**
870.3150 (82-1(b)) Subchronic Feeding in Dogs (90 days)	00099130 Sherman et al. 1970 Unacceptable guideline M: 0, 2.7, 14.4, or 40.7 F: 0, 2.7, 11.3, or 35 (0, 100, 500 or 1500/2500 ppm)	**53% a.i. carbendazim** NOAEL: 11.3 (F), 14.4 (M) LOAEL: 35 (F), 40.7 (M) based on histopathology changes in liver (1/4 males and 1/4 females) and testes (1/4 males) and increased alkaline phosphatase, cholesterol and SGPT. Liver effects included hepatic cirrhosis (hepatic cell necrosis, tubular collapse, and increased fibrous connective tissue around triads). Decreased testes weight in 3/4 males in the high dose.
870.4100 870.4200 (83-1& 2) Chronic feeding/ carcinogenicity study in CD rats (2 yrs)	00088333, 00068982, Accession #: 2328700, 232871 Sherman et al. 1972, Lee 1978 Minimum 0, 5, 25, 250 or 125/500 (430) [0, 100, 500, 5000 or 2500/10000 (8557) ppm]	**53% a.i. carbendazim** NOAEL:25 LOAEL: 250 based on statistically significant decreases in red blood cell parameters (hematocrit, hemoglobin an red blood cells) in females and histological lesions in the liver (cholangiohepatitis and pericholangitis) in males and females. No evidence of carcinogenicity. <u>Deficiencies</u>: Only 36 rats/sex/dose tested (only 20 rats/sex were in 250 mg/kg/day dose group). Lack of complete clinical chemistry data and histopathology examination. At 24 months, only liver evaluated in 5 and 25 mg/kg/day groups and only liver, kidney and testes evaluated in 250 mg/kg/day group.
870.4100b (83-1b) Chronic feeding study in beagle dogs (2 yrs)	00088333 Accession #: 232870-0, 232871 (Sherman et al. 1972) Acceptable guideline 0, 2.5, 12.5, or 37.5/62.5 (0, 100, 500 and 1500/2500 ppm) (Doses adjusted for % a.i.)	**53% a.i. carbendazim** NOAEL: 2.5 LOAEL: 12.5 based on swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis and biochemical alterations indicative of liver damage (i.e., increased cholesterol, total protein, SGPT and alkaline phosphatase levels, and decreased A/G ratio). At 37.5/62.5 mg/kg/day, anorexia, distended abdomens and poor nutritional condition were reported.
870.4100b (83-1b) Chronic feeding study in beagle dogs (1 yr)	00164304 Accession # 265664 (Stadler et al. 1986) Acceptable guideline F:0, 2.93, 6.43 or 16.54 mg/kg M: 0, 3.2, 7.19, 17.07 (0, 100, 200, or 500 ppm)	**98.8% a.i. carbendazim** NOAEL: 6.43 (200 ppm) LOAEL: 16.54 (500 ppm) based on possible transient increase in cholesterol (males and females) consistent with previous dog feeding studies.

Table A-2. Toxicity Studies for MBC		
GDLN/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day) (1)**
870.4200b (83-2b), 83-1 Chronic feeding study in CD-1 mice (2 yrs)	00096513, 00154676 256028, and 256029 Wood et al. 1982, Schneider, Wood and Hall 1982 Core Grade: acceptable guideline. The study was designed to specifically evaluate the liver carcinogenicity potential of MBC 0, 75, 225, 1125 (females) or 1125/563 (males) (0, 500, 1500 or 7500 (females) or 7500/3750 (males) ppm)	**99.3% a.i. carbendazim** NOAEL (non-cancer systemic): 75 LOAEL (non-cancer systemic): 225 based on liver toxicity (hepatocellular necrosis and swelling), body weight decrease and lymphoid depletion. In both sexes, there was an increased incidence of liver tumors. In males, hepatocellular carcinomas were noted at 225 mg/kg/day, while females exhibited carcinomas and adenomas at all dose levels. Note: The 7500 ppm was reduced to 3750 ppm at 66 weeks in males due to increased mortality.
870.4200b (83-2b) Chronic feeding/ carcinogenicity study in NMRKf mice (2 years)	00154679 Accession # 2560302 (Donaubauer et al. 1982) Unacceptable guideline 0; 5.8-7.1; 17.1 -21.2; 34.4 - 41.9 or 522 - 648 (0, 50, 150, 300 or 1000/5000 ppm).	**99% a.i. carbendazim** NOAEL (non-cancer systemic): 34.4 - 41.9 LOAEL (non-cancer systemic): 522 - 648 based on increases the incidences of hepatic cell hypertrophy, clear cell foci and hepatocellular necrosis. No increased incidence of carcinogenicity was noted. Deficiencies: incomplete examination of most recommended tissues, blood and urine were not collected for analysis.
870.4200b (83-2) Chronic feeding/ carcinogenicity study in Swiss mice (80 weeks)	00153420 Accession # 256029 (Beems et al. 1976) Unacceptable guideline 0, 22.5, 45 or 750 (0, 150, 300 or 5000 ppm)	**99% a.i. carbendazim** NOAEL:45 LOAEL:750 based on hepatic alterations which included increased relative liver weights in both sexes, increased number of foci of cellular alterations in the liver in females, neoplastic nodules in females and hepatoblastomas in males Deficiencies: Brief methods, there were no historical data or microscopic or gross pathology reports for individual animals, and there was no assurance that the diets were analyzed for compound homogeneity and stability. In addition, there were no hematology or clinical chemistry analysis, nor urinalysis. Only organs or lesions suspected of being tumors and livers (2 sections) were examined histologically.
870.3700a (83-3a) Developmental Study in Crl:CE BR rats (gavage)	40438001 Alvarez 1987 Acceptable guideline 0, 10, 20, 90 gestation day 7-16	**98.8% a.i. carbendazim** Maternal NOAEL: 20 Maternal LOAEL:90 (increased absolute liver weight) Developmental NOAEL:10 Developmental LOAEL: 20 based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations.

Table A-2. Toxicity Studies for MBC		
GDLN/ STUDY	**MRID NO. (YEAR)/ CLASSIFICATION/ DOSES (mg/kg/day) (1)**	**RESULTS (mg/kg/day) (1)**
870.3700b (83-3b) Developmental Study in New Zealand White Rabbits (gavage)	Accession # 260571 (Christian et al. 1985) Acceptable guideline 0, 10, 20 or 125 gestation day 7-19	**98.7% a.i. carbendazim** Maternal NOAEL: 20 Maternal LOAEL:125 (abortions and decreased body weight) Developmental NOAEL:10 Developmental LOAEL: 20 mg/kg/day based on decreased implantations and litter size, and increased resorptions. Malformations (fused ribs, and malformed cervical vertebrae) were noted at 125 mg/kg/day
870.3800 (83-4) Reproductive Study in ChR-CD rats (diet)	00088333 Sherman et al. 1972 Unacceptable guideline 0, 5, 25, 250 or 125/500 (0, 100, 500, 5000 or 2500/10,000 ppm)	**50 or 70% a.i. carbendazim** Reproductive NOAEL:25 Reproductive LOAEL: 250 based on toxic signs of decreased pup weight noted at weaning. Deficiencies: Litter (or fetal) weights were not measured at birth, therefore it is impossible to attribute weight decrease in 5000 and 2500/10000 ppm groups to prenatal or lactation period. Only 16 dams (20 dams for 5000 ppm), resulting in 10-16 litters per group were available, rather than the 20 litters recommended in the guideline. There was no special attention for the testes, a known target organ, including organ weights measurements.
NA Single dose (gavage) rat study	Nakai et al. (1982) Literature Study 0, 50, 100, 200, 400 or 800 mg/kg	NOAEL: none observed LOAEL: 50 based on premature release of immature germ cells 2 days post exposure, and atrophy of a few seminiferous tubules and significant decrease in seminiferous tubule diameter 70 days post exposure.

(1) Unless specified, mg ai MBC/kg/day.
NOAEL = No Observable Adverse Effect Level
LOAEL = Lowest Observable Adverse Effect Level